effect of vanadate (IC50, 5.0 +/- 0.4 micromol/l). After vanadate treatment, a phosphorylated P55 protein is immunoprecipitated by antibodies to both phosphotyrosine and phosphatidylinositol (PI) 3-**kinase**. In conclusion, rat adipocytes contain an additional vanadate-activatable nonreceptor membranous protein tyrosine **kinase** that may participate in the effects of vanadate not carried out by CytPTK. We also suggest that after treatment with vanadate, MembPTK is activated by autophosphorylation and interacts with PI 3-**kinase** . This may explain how vanadate activates PI 3-**kinase** without involving receptor activation and IRS-1 phosphorylation.

9/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11022010 97375484 PMID: 9231801
Phosphoinositolglycan-peptides from yeast potently induce metabolic **insulin** actions in isolated rat adipocytes, cardiomyocytes, and diaphragms.
Muller G; Wied S; Crecelius A; Kessler A; Eckel J
Hoechst AG, Hoechst Marion Roussel, Frankfurt am Main, Germany.
Endocrinology (UNITED STATES) Aug **1997**, 138 (8) p3459-75,
ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Polar headgroups of free glycosyl-phosphatidylinositol (GPI) lipids or protein-bound GPI membrane anchors have been shown to exhibit **insulin** -mimetic activity in different cell types. However, elucidation of the molecular mode of action of these phospho-inositolglycan (PIG) molecules has been hampered by 1) lack of knowledge of their exact structure; 2) variable action profiles; and 3) rather modest effects. In the present study, these problems were circumvented by preparation of PIG-peptides (PIG-P) in sufficient quantity by sequential proteolytic (V8 protease) and lipolytic (phosphatidylinositol-specific phospholipase C) cleavage of the GPI-anchored plasma membrane protein, Gce1p, from the yeast Saccharomyces cerevisiae. The structure of the resulting PIG-P, NH2-Tyr-Cys-Asn-ethanolamine-PO4-6(Man1-2)Man1-2Man1-+ ++6Man1-4GlcNH(2)1-6 myo-inositol-1,2-cyclicPO4, was revealed by amino acid analysis and Dionex exchange chromatography of fragments generated enzymatically or chemically from the neutral glycan core and is in accordance with the known consensus structures of yeast GPI anchors. PIG-P stimulated glucose transport and lipogenesis in normal, desensitized and receptor-depleted isolated rat adipocytes, increased glycerol-3-phosphate acyltransferase activity and translocation of the glucose transporter isoform 4, and **inhibited** isoproterenol-induced **lipolysis** and protein **kinase** A activation in adipocytes. Furthermore, PIG-P was found to stimulate glucose transport in isolated rat cardiomyocytes and glycogenesis and glycogen synthase in isolated rat diaphragms. The concentration-dependent effects of the PIG-P reached 70-90% of the maximal **insulin** activity with EC50-values of 0.5-5 microM. Chemical or enzymic cleavages within the glycan or peptide portion of the PIG-P led to decrease or loss of activity. The data demonstrate that PIG-P exhibits a potent **insulin**-mimetic activity which covers a broad spectrum of metabolic **insulin** actions on glucose transport and metabolism.

9/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10955132 97307669 PMID: 9165011

Antilipolytic actions of vanadate and **insulin** in rat adipocytes mediated by distinctly different mechanisms.

Li J; Elberg G; Sekar N; bin He Z; Shechter Y

Department of Biochemistry, The Weizmann Institute of Science, Rehovot, Israel.

Endocrinology (UNITED STATES) Jun **1997**, 138 (6) p2274-9, ISSN 0013-7227 Journal Code: 0375040

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Vanadate, which mimics the biological effects of **insulin**, also **inhibits lipolysis** in rat adipocytes. Here we demonstrate that the antilipolytic effect of vanadate differs from that of **insulin** at least by the five following criteria: 1) vanadate **inhibits lipolysis** mediated by high (supraphysiological) concentrations of catecholamines; 2) vanadate antagonizes (Bu)2cAMP-mediated **lipolysis**; 3) vanadate antagonizes isobutylmethylxanthine-dependent **lipolysis**, 4) vanadate **inhibits lipolysis** mediated by okadaic acid; and 5) wortmannin, which blocks the antilipolytic effect of **insulin**, fails to block vanadate-mediated antilipolysis. Vanadate does activate phosphoinositol 3-**kinase**, and wortmannin blocks this activation. Our working hypothesis assumes that all of the **insulin**-like effects of vanadate, including antilipolysis, are initiated by the **inhibition** of protein phosphotyrosine phosphatases (PTPases). Among documented PTPase **inhibitors** we found that VOSO4 (oxidation state +4), several organic vanadyl compounds (+4), zinc (Zn2+), tungstate (W), and molybdate (Mo) also had antilipolytic activity. The order of potency was vanadyl acetylacetonate > or = VOSO4 > or = NaVO3 > or = vanadyl-dipicolinate > Zn2+ >> W > Mo, and it correlated better with the **inhibition** of adipose membranal-PTPases in cell-free experiments. We have concluded that the antilipolytic effect of vanadate is 1) mechanistically distinct from that of **insulin**, 2) independent of phosphoinositol 3-**kinase** activation, and 3) independent of the lipolytic cascade. We also strongly suggest that the antilipolytic effect of vanadate emanates from **inhibiting** adipose membranal, rather than cytosolic PTPases, and present preliminary data showing distinct differences in catalysis between these two PTPase categories. Overall, the study indicates that antilipolysis can be manifested via alternative, **insulin**-independent, signal-transducing pathways.

9/3,AB/11 (Item 11 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

10904778 97256776 PMID: 9099705

Leptin impairs metabolic actions of **insulin** in isolated rat adipocytes.

Muller G; Ertl J; Gerl M; Preibisch G

Hoechst AG, HMR, Research Area Frankfurt, D-65926 Frankfurt, Federal Republic of Germany.

Journal of biological chemistry (UNITED STATES) Apr 18 **1997**, 272 (16) p10585-93, ISSN 0021-9258 Journal Code: 2985121R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Leptin is an adipocyte hormone involved in the regulation of energy homeostasis. Generally accepted biological effects of leptin are **inhibition** of food intake and stimulation of metabolic rate in ob/ob mice that are defective in the leptin gene. In contrast to these centrally mediated effects of leptin, we are reporting here on leptin effects on isolated rat adipocytes. Leptin impairs several metabolic actions of

insulin , i.e. stimulation of glucose transport, glycogen synthase, lipogenesis, **inhibition** of isoproterenol-induced **lipolysis**, and protein **kinase** A activation, as well as stimulation of protein synthesis. **Insulin** effects were reduced by leptin (2 nM) with a half-life of about 8 h. At low leptin concentrations (<1 nM), the **insulin** sensitivity was reduced leading to a shift to the right in the dose-response curve. At higher concentrations the responsiveness was diminished, resulting in nearly complete **inhibition** of **insulin** effects at >30 nM leptin. The IC50 value of leptin was 3.1 +/- 1 nM after 15 h of preincubation of adipocytes in primary culture. The natural splice variant des-Gln49-leptin exhibited a significantly lower potency. Adipocytes regained full **insulin** sensitivity within a few hours after leptin removal. The stimulation of glucose transport by vanadate was not affected by leptin. These data show specific and potent impairment of **insulin** action by leptin in the physiological concentration range of both leptin and **insulin**, which may be related to the pathophysiology of **insulin** resistance in both non-**insulin**-dependent diabetes mellitus and obesity.

9/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10866720 97218198 PMID: 9065430

Regulation of protein **kinase** B and glycogen synthase **kinase**-3 by **insulin** and beta-adrenergic agonists in rat epididymal fat cells. Activation of protein **kinase** B by wortmannin-sensitive and -insensitive mechanisms.

Moule S K; Welsh G I; Edgell N J; Foulstone E J; Proud C G; Denton R M
Department of Biochemistry, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, United Kingdom.

Journal of biological chemistry (UNITED STATES) Mar 21 **1997**, 272 (12) p7713-9, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Previous studies using L6 myotubes have suggested that glycogen synthase **kinase**-3 (GSK-3) is phosphorylated and inactivated in response to **insulin** by protein **kinase** B (PKB, also known as Akt or RAC) (Cross, D. A. E., Alessi, D. R., Cohen, P., Andjelkovic, M., and Hemmings, B. A. (1995) Nature 378, 785-789). In the present study, marked increases in the activity of PKB have been shown to occur in **insulin**-treated rat epididymal fat cells with a time course compatible with the observed decrease in GSK-3 activity. Isoproterenol, acting primarily through beta3-adrenoreceptors, was found to decrease GSK-3 activity to a similar extent (approximately 50%) to **insulin**. However, unlike the effect of **insulin**, the **inhibition** of GSK by isoproterenol was not found to be sensitive to **inhibition** by the phosphatidylinositol 3'-**kinase inhibitors**, wortmannin or LY 294002. The change in GSK-3 activity brought about by isoproterenol could not be mimicked by the addition of permeant cyclic AMP analogues or forskolin to the cells, although at the concentrations used, these agents were able to stimulate **lipolysis**. Isoproterenol, but again not the cyclic AMP analogues, was found to increase the activity of PKB, although to a lesser extent than **insulin** . While wortmannin abolished the stimulation of PKB activity by **insulin**, it was without effect on the activation seen in response to isoproterenol. The activation of PKB by isoproterenol was not accompanied by any detectable change in the electrophoretic mobility of the protein on SDS-polyacrylamide gel electrophoresis. It would therefore appear that distinct mechanisms exist for the stimulation of PKB by **insulin** and isoproterenol in rat fat cells.

9/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10701344 97050601 PMID: 8895329
Effects of tyrosine **kinase inhibitors** on tyrosine phosphorylations and the **insulin**-like effects in response to human growth hormone in isolated rat adipocytes.
Ridderstrale M; Tornqvist H
Department of Pediatrics, University of Lund, Sweden.
Endocrinology (UNITED STATES) Nov **1996**, 137 (11) p4650-6,
ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent data suggest involvement of the Janus tyrosine **kinase**-2 (JAK2) in human GH-induced tyrosine phosphorylation of the GH receptor and the **insulin** receptor substrates 1 and 2 (IRS-1 and IRS-2), leading to activation of the phosphatidylinositol 3-**kinase** and the acute **insulin** -like effects in primary rat adipocytes. To investigate the functional role of this **kinase**, we screened a number of tyrosine **kinase inhibitors** for their ability to **inhibit** three rapid effects of GH on primary adipocytes: increased lipogenesis, **inhibition** of noradrenaline-induced **lipolysis**, and promotion of JAK2 tyrosine phosphorylation. Only staurosporine was found to **inhibit** all three effects. The **inhibition** of lipogenesis and antilipolysis exhibited the same staurosporine dose dependency (IC50, approximately 40 nM) as **inhibition** of JAK2 and IRS-1 tyrosine phosphorylation as well as binding of the p85 subunit of phosphatidylinositol 3-**kinase** to IRS-1 and IRS-2. The unidentified cytosolic tyrosine-phosphorylated protein pp95, in contrast, was not affected, suggesting that it is not phosphorylated primarily by JAK2. Protein **kinase** C does not seem to be directly involved in the **insulin**-like effects, because the selective protein **kinase** C **inhibitor** calphostin C had no effect at levels up to 100 nM above which unspecific cellular effects occurred. Methyl-2,5-dihydroxy cinnamate **inhibited** GH-induced lipogenesis from [3-3H]glucose and nonstimulated lipogenesis from [2-14C]-pyruvate and [3H]acetate, but was without effect on GH-induced 2-deoxy-D-[1-3H]glucose uptake, JAK2 phosphorylation and antilipolysis, suggesting unspecific effects on mitochondrial metabolism rather than a direct effect on the GH-mediated signal. Tyrphostin 25 and herbimycin A had no effect on any of the parameters studied, except for a slight increase in JAK2 phosphorylation in response to tyrphostin 25. In summary, these data support the role for JAK2 in mediating the **insulin**-like effects of GH in adipocytes.

9/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10608580 96426181 PMID: 8828475
The antilipolytic effects of **insulin** and epidermal growth factor in rat adipocytes are mediated by different mechanisms.
Tebar F; Soley M; Ramirez I
Department de Bioquimica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, Spain.
Endocrinology (UNITED STATES) Oct **1996**, 137 (10) p4181-8,
ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
Epidermal growth factor (EGF) and **insulin** induced similar effects in isolated rat adipocytes. To determine whether EGF and **insulin** produced similar effects through the same mechanisms, we focused on **lipolysis**. **Insulin inhibited** the **lipolysis** stimulated by isoproterenol, glucagon (either alone or in combination with adenosine deaminase), adenosine deaminase itself, or forskolin. In contrast, EGF did not **inhibit** the **lipolysis** stimulated by forskolin or by hormones when the cells were also incubated with adenosine deaminase. The effect of **insulin**, but not that of EGF, on isoproterenol-stimulated **lipolysis** disappeared when adipocytes were incubated with 1 microM wortmannin. These results indicate that EGF and **insulin** affected **lipolysis** through different mechanisms. We observed that EGF, but not **insulin**, increased cytosolic Ca2+. The effect of EGF, but not that of **insulin**, disappeared when the cells were incubated in a Ca2+-free medium. We suggest that EGF, but not **insulin**, mediate its antilipolytic effect through a Ca2+-dependent mechanism which, however, do not involve Ca2+-activated protein **kinase** C isoforms. This is based on the following: 1) phorbol 12-myristate 13-acetate affected **lipolysis** in an opposite way to that of EGF; and 2) the protein **kinase** C **inhibitor** bisindolylmaleimide GF 109203X did not affect the antilipolytic action of EGF. Our results indicate that the antilipolytic effect of EGF resembles more that of vasopressin than that of **insulin**.

9/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10586645 96401514 PMID: 8927028
Evidence for selective effects of vanadium on adipose cell metabolism involving actions on cAMP-dependent protein **kinase**.
Brownsey R W; Dong G W
Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, Canada.
Molecular and cellular biochemistry (NETHERLANDS) Dec 6-20 **1995**, 153 (1-2) p131-7, ISSN 0300-8177 Journal Code: 0364456
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **insulin**-like effects of vanadium in vivo are likely to be achieved at micromolar concentrations. Demonstrated effects of vanadium on adipose tissue of streptozotocin-diabetic rats include **inhibition** of basal and stimulated rates of **lipolysis** and effects on fat cell protein phosphorylation. The studies described below examined the effects of vanadium (to a maximum concentration of 0.5 mM) on adipose cells or tissue in vitro. Vanadium, added as a vanadyl-albumin complex or as sodium orthovanadate, produced a marked (greater than 50%) **inhibition** of isoproterenol-stimulated **lipolysis**. **Inhibition** of **lipolysis** equivalent to that seen with **insulin**, was achieved with approximately 100 microM vanadium. In contrast, no **insulin**-like stimulation of de novo fatty acid biosynthesis was observed with vanadium below 0.5 mM. Surprisingly, the antilipolytic effects of vanadium persisted in the presence of cilostamide, an **inhibitor** of the **insulin**-sensitive isoform of cyclic nucleotide phosphodiesterase. Studies with purified preparations of the catalytic subunit of cyclic AMP-dependent protein **kinase** revealed dose-dependent **inhibition** with vanadyl-glutathione (to a maximum of approximately 40% **inhibition**). Equivalent **inhibition** of cyclic AMP-dependent phosphorylation of Kemptide (approximately 50%) was observed upon incubation of freshly-prepared fat-pad supernatant fractions with vanadyl-glutathione. These results suggest that effects of low concentrations of vanadium may be

mediated, at least in part, by actions on the catalytic subunit of cyclic AMP-dependent protein **kinase**.

9/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10561747 96373629 PMID: 8779920
Insulin sensitizes beta-agonist and forskolin-stimulated **lipolysis** to **inhibition** by 2',5'-dideoxyadenosine.
Gokmen-Polar Y; Coronel E C; Bahouth S W; Fain J N
Department of Biochemistry, University of Tennessee, Memphis 38163, USA.
American journal of physiology (UNITED STATES) Feb **1996**, 270 (2 Pt 1) pC562-9, ISSN 0002-9513 Journal Code: 0370511
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In isolated rat adipocytes incubated in the absence of **insulin**, 2',5'-dideoxyadenosine blocked the increase in total adenosine 3',5'-cyclic monophosphate (cAMP) accumulation due to beta 1- or beta 3-catecholamine agonists and forskolin without affecting their stimulation of **lipolysis**. The **inhibition** of cAMP accumulation by 2',5'-dideoxyadenosine was not reflected in the total cytosolic cAMP-dependent protein **kinase** A activity, suggesting that the **inhibition** of cAMP occurred in cellular compartments distinct from those involved in the regulation of bulk protein **kinase** A activity. However, there was a good correlation between effects of lipolytic agents on cytosolic protein **kinase** A activity in fat cell extracts and **lipolysis**. Furthermore, it was possible to see an **inhibition** of the increase due to beta-agonists in cAMP accumulation, protein **kinase** A activity, and **lipolysis** by 2',5'-dideoxyadenosine in the presence of **insulin** . These data suggest that the readily measurable accumulation of cAMP seen with catecholamines in the absence of **insulin** is in a compartment separate from that involved in protein **kinase** A activation.

9/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10543887 96355505 PMID: 8702915
Insulin signaling in mice expressing reduced levels of Syp.
Arrandale J M; Gore-Willse A; Rocks S; Ren J M; Zhu J; Davis A; Livingston J N; Rabin D U
Bayer Corporation, Pharmaceutical Division, Metabolic Disorders Research, West Haven, Connecticut 06516, USA.
Journal of biological chemistry (UNITED STATES) Aug 30 **1996**, 271 (35) p21353-8, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Syp is a protein tyrosine phosphatase implicated in **insulin** and growth factor signaling. To evaluate the role of syp in **insulin**'s regulation of plasma glucose, we generated knockout mice. Homozygous knockout mice die prior to day 10.5 of embryonic development. Hemizygous mice express half the levels of syp protein compared with their wild type littermates but do not display any gross morphological changes. Total body weight (age 2-10 weeks) and plasma **insulin** and glucose levels both in fasting and glucose-challenged states were comparable in the wild type and the hemizygous mice. No differences were observed in **insulin**-induced

glucose uptake in soleus muscle and epididymal fat; **insulin** **inhibition** of **lipolysis** was also similar. We injected **insulin** into the portal vein of the mice to examine upstream events of the **insulin** signaling cascade. Tyrosine phosphorylation of **insulin** receptor and **insulin** receptor substrate-1 (IRS-1) from hemizygous tissue was similar to that of wild type tissue. Association of the p85 subunit of phosphatidylinositol 3-**kinase** to IRS-1 increased an average of 2-fold in both groups. We did not observe an increase of IRS-1/syp association after **insulin** administration, but we did note a significant basal association in both wild type and hemizygous tissue. Our results do not support a major role for syp in the acute in vivo metabolic actions of **insulin**.

9/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10540869 96352287 PMID: 8720602
Mechanism of anti-lipolytic action of acipimox in isolated rat adipocytes.
Christie A W; McCormick D K; Emmison N; Kraemer F B; Alberti K G; Yeaman S J
Department of Biochemistry and Genetics, University of Newcastle upon Tyne, UK.
Diabetologia (GERMANY) Jan **1996**, 39 (1) p45-53, ISSN 0012-186X Journal Code: 0006777
Contract/Grant No.: DK 46942; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Acipimox is commonly used to treat hypertriglyceridaemia in non-**insulin** -dependent diabetic patients, but its precise mechanism of action has yet to be elucidated. We examined the in vitro effects of acipimox on the lipolytic regulatory cascade in epididymal adipocytes isolated from Wistar rats. Acipimox **inhibited** the lipolytic rate stimulated by adenosine deaminase (1 U/ml) in a concentration-dependent manner, reaching a near-basal value at 10 mumol/l acipimox. **Lipolysis** activated by sub-maximal levels of isoproterenol in combination with adenosine deaminase (20 mU/ml) was significantly ($p < 0.05$) decreased by 100 mumol/l acipimox, whereas, in the absence of adenosine deaminase, 100 mumol/l acipimox showed no significant ($p > 0.05$) **inhibition**. These findings suggested that the anti-lipolytic mechanism regulated by adenosine may also be regulated by acipimox. Acipimox diminished the intracellular cyclic AMP level produced by 25 nmol/l isoproterenol in the presence of adenosine deaminase (20 mU/ml) in a concentration-dependent manner. At the same level of stimulation, acipimox **inhibited** the cyclic AMP-dependent protein **kinase** activity ratio and lipolytic rate over the same concentration range, with significant ($p < 0.05$) reductions occurring at and above, 0.5 mumol/l and 10 mumol/l acipimox, respectively. Western blotting showed that upon lipolytic stimulation (1 U/ml adenosine deaminase; 100 nmol/l isoproterenol) a threefold increase in the lipolytic rate was accompanied by a significant ($p < 0.05$) rise in hormone-sensitive lipase associated with the lipid fraction. Acipimox (1 mmol/l) and **insulin** (1 nmol/l) re-distributed hormone-sensitive lipase back to the cytosol, with a corresponding significant ($p < 0.05$) loss from the fat cake fraction of adipocyte homogenates. In conclusion, the anti-lipolytic action of acipimox is mediated through suppression of intracellular cyclic AMP levels, with the subsequent decrease in cyclic AMP-dependent protein **kinase** activity, leading to the reduced association of hormone-sensitive lipase with triacylglycerol substrate in the lipid droplet of adipocytes.

9/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10532439 96343837 PMID: 8756584
The beta 3-adrenergic receptor **inhibits insulin**-stimulated leptin secretion from isolated rat adipocytes.
Gettys T W; Harkness P J; Watson P M
Department of Medicine, Medical University of South Carolina, Charleston 29425, USA.
Endocrinology (UNITED STATES) Sep **1996**, 137 (9) p4054-7, ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: DK42486; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Various model systems have been used to study the expression of the recently cloned ob gene, leptin. Here we report that freshly isolated rat white adipocytes incubated with **insulin** release leptin in a rapid and concentration-dependent manner (EC50 of 0.221 +/- .075 nM). **Insulin** -stimulated leptin release could be detected as early as 30 min and a maximal 2-3 fold effect was produced by 10 nM **insulin**. The effect of **insulin** was completely blocked by simultaneous activation of cAMP-dependent protein **kinase**. Using the activation of **lipolysis** as an index of cAMP-dependent protein **kinase** activity, we show that **inhibition** of leptin release by norepinephrine or the selective beta 3-adrenergic receptor agonist, CL316,243, occurred in parallel to activation of cAMP-dependent protein **kinase** . In addition, beta 1- and beta 2-adrenergic receptor antagonists did not impair the ability of norepinephrine or CL316,243 to **inhibit** leptin release from the adipocytes. These findings suggest that the beta 3-adrenergic receptor plays a central role in regulating the release of leptin from the adipocyte.

9/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10523891 96334996 PMID: 8708554
GH **inhibition** of lipogenesis and stimulation of **lipolysis** in sheep adipose tissue: involvement of protein serine phosphorylation and dephosphorylation and phospholipase C.
Vernon R G
Hannah Research Institute, Ay, UK.
Journal of endocrinology (ENGLAND) Jul **1996**, 150 (1) p129-40, ISSN 0022-0795 Journal Code: 0375363
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The intracellular signalling systems involved in the chronic **insulin** -antagonistic, anti-lipogenic effects and also the lipolytic effect of GH have been investigated in sheep adipose tissue in an in vitro tissue culture system. During culture, chronic exposure to GH decreased the rate of lipogenesis and prevented the increase in lipogenesis induced by **insulin** . GH also increased glycerol release into the culture medium. GH had no acute, **insulin**-like effect on lipogenesis in sheep adipose tissue. Pretreatment with phorbol ester to down-regulate isoforms of protein **kinase** C or addition of the protein serine **kinase** **inhibitor** staurosporine decreased the anti-lipogenic effect of GH while the protein serine **kinase** **inhibitor** H7 eliminated it

completely. Pretreatment with phorbol ester or addition of H7 also decreased the **insulin** -antagonistic effect of GH on lipogenesis. Addition of the protein serine phosphatase **inhibitor** okadaic acid or the phosphatidyl choline phospholipase C **inhibitor** D609 both diminished the anti-lipogenic and **insulin**-antagonistic effects of GH. Chronic exposure of adipose tissue to GH had no effect on the total activity of acetyl CoA carboxylase or its activation status but it did diminish the increase in activation status induced by **insulin**. H7 and okadaic acid also diminished the increase in activation status of acetyl CoA carboxylase induced by **insulin** but did not alter the effect of GH on this variable. Okadaic acid decreased total acetyl CoA carboxylase activity. Pretreatment with phorbol ester or the addition of H7, staurosporine or okadaic acid increased glycerol release into the culture medium to the same extent as GH itself; the effects of GH and these various agents were not additive. These studies suggest that the anti-lipogenic, **insulin**-antagonistic effects of GH involve both protein serine **kinases** and phosphatases, possibly including one or more isoforms of protein **kinase** C, and a phosphatidyl choline-specific phospholipase C. Comparison with studies by others on the GH enhancement of preadipocyte differentiation and prolactin stimulation of lipogenesis in mammary tissue suggests involvement of protein **kinase** C at an early stage in all three systems. In contrast, effects of okadaic acid vary with the system, suggesting the involvement of protein serine phosphatase activity in a late stage of the action of GH. The effects of GH on lipogenesis and **lipolysis** do not occur via identical mechanisms.

9/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10503245 96313826 PMID: 8703991

Phenylarsine oxide and vanadate: apparent paradox of **inhibition** of protein phosphotyrosine phosphatases in rat adipocytes.

Li J; Elberg G; Shechter Y
Department of Biochemistry, Weizmann Institute of Science, Rehovot, Israel.

Biochimica et biophysica acta (NETHERLANDS) Jul 24 **1996**, 1312 (3) p223-30, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Vanadate mimics, whereas phenylarsine oxide (PAO) antagonizes, the effects of **insulin** in rat adipocytes. Both vanadate and PAO are documented **inhibitors** of protein-phosphotyrosine phosphatases. The relationship between the **inhibition** of '**inhibitory**' PTPase and 'stimulatory' PTPase has been studied here in primary rat adipocytes. Low concentrations of PAO (IC50 = 0.6-2.0 microM) blocked the stimulating effects of **insulin** , vanadate and pervanadate on hexose uptake and glucose metabolism. **Inhibition** of isoproterenol-mediating **lipolysis** by vanadate and **insulin** was not blocked by PAO. The activating effects of okadaic acid on hexose uptake and glucose metabolism, which occur at points downstream to tyrosine phosphorylation, were also not blocked by PAO. Subsequent studies suggested that the PAO-sensitive PTPase comprises a minute fraction of the total adipocytic PTPase activity. To identify its location we applied procedures involving fractionations and activation of non-receptor adipocytic protein tyrosine **kinase** by PAO and vanadate in cell free assays. We found that the '**inhibitory**' PTPase is exclusively associated with the membrane fraction whereas the 'stimulatory' PTPases are present in both the cytosolic and plasma membrane compartments. We next searched for markers, possibly associated with PAO-dependent desensitization and found that several proteins became phosphorylated on tyrosine moieties in the supernatant of PAO but not in

vanadate pretreated adipocytes. In summary, we propose the presence of a minute, plasma membrane associated PTPase in primary rat adipocytes, **inhibition** of which arrests the activation of glucose metabolism. In contrast, **inhibition** of all the other cellular adipose PTPases, ultimately activates rather than **inhibits** these same bioeffects.

9/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10445005 96251701 PMID: 8649343
Enhanced desensitization and phosphorylation of the beta 1-adrenergic receptor in rat adipocytes by peroxovanadate.
Bahouth S W; Gokmen-Polar Y; Coronel E C; Fain J N
Department of Pharmacology, University of Tennessee, Memphis, 38163, USA.
Molecular pharmacology (UNITED STATES) Jun **1996**, 49 (6) p1049-57, ISSN 0026-895X Journal Code: 0035623
Contract/Grant No.: HL48169; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Peroxovanadate (PVN) is an **insulin**-like agent that **inhibits** the dephosphorylation of the **insulin** receptor **kinase**. PVN **inhibited** the lipolytic action of 0.1 microM isoproterenol by 88%, which is a relatively specific beta 1 catecholamine agonist at this concentration, but was largely ineffective against beta 3 agonists or forskolin. To determine whether PVN-mediated desensitization of the beta 1 AR was associated with enhanced phosphorylation, we immunoprecipitated the beta 1 AR from rat adipocytes that were metabolically labeled with 32PO4. Isoproterenol enhanced the net phosphorylation of the beta 1 AR by 8 +/- 2-fold over control. PVN increased the net phosphorylation of the beta 1 AR by 5 +/- 0.5-fold, and together with isoproterenol, they enhanced the phosphorylation of the beta 1 AR by 2-fold over isoproterenol alone. Phosphoamino acid analysis of the phosphorylated receptor revealed phosphate incorporation into serine that was proportional to the radioactivity incorporated into the immunoprecipitated receptor. PVN **inhibited** the serine/threonine phosphatase calcineurin, suggesting that **inhibition** of receptor dephosphorylation may play a role in the actions of PVN. Cyanogen bromide cleavage of the phosphorylated beta 1 AR generated a phosphoprotein with a molecular mass consistent with carboxyl-terminal phosphorylation. Furthermore, the magnitude of receptor phosphorylation by isoproterenol was 3-fold larger than that due to forskolin, suggesting that beta 1 AR is a substrate for the beta AR **kinase** that phosphorylates carboxyl-terminal residues in the beta(2) AR. Our findings suggest that PVN may be a powerful new tool with which to study the phosphorylation of other G protein-coupled receptors.

9/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10412305 96218603 PMID: 8635677
A stable peroxovanadium compound with **insulin**-like action in human fat cells.
Eriksson J W; Lonnroth P; Posner B I; Shaver A; Wesslau C; Smith U P
Lundberg Laboratory for Diabetes Research, Department of Internal Medicine, Sahlgrenska University Hospital, Goteborg, Sweden.
Diabetologia (GERMANY) Feb **1996**, 39 (2) p235-42, ISSN 0012-186X Journal Code: 0006777
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
Aqueous solutions of peroxovanadium (pV) compounds are potent **insulin** -mimics in various types of cell. Since chemical instability is a problem with these agents, we studied the **insulin**-like action in human fat cells of a stable pV complex, bpV(pic). It enhanced 14C-U-glucose uptake in a dose-dependent manner by approximately twofold which was slightly less than the effect of **insulin** (approximately threefold). The pV complex did not alter cell-surface **insulin** binding and submaximal concentrations did not influence cellular sensitivity to **insulin** action on glucose uptake. The bpV(pic) **inhibited** the lipolytic effect of isoprenaline to the same extent as **insulin**; however, when the cGMP-**inhibitable** low-K(m) phosphodiesterase (cGI-PDE) was blocked with the specific **inhibitor** OPC 3911, the antilipolytic effect of **insulin** , but not that of bpV(pic), was completely prevented. Moreover, when **lipolysis** was stimulated by the non-hydrolysable cAMP analogue N6-monobutyryl cAMP, bpV(pic), in contrast to **insulin** , maintained an antilipolytic effect. These findings indicate that bpV(pic) exerts its antilipolytic effect not only through cGI-PDE activation, similar to the effect of **insulin**, but also by means of other mechanisms. The tyrosine **kinase** activity of **insulin** receptors from human placenta was not altered by the pV compound itself, whereas bpV(pic) clearly enhanced **insulin**-stimulated activity. In contrast, in situ tyrosine phosphorylation of the **insulin** receptor beta-subunit as well as that of several other proteins was clearly increased in cells which were treated with bpV(pic), whereas vanadate only amplified **insulin** -stimulated tyrosine phosphorylation. In conclusion, bpV(pic) exerts powerful **insulin**-like effects in human fat cells and may be a new and potentially useful agent in the management of **insulin**-resistant states.

9/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10412285 96218583 PMID: 8646851
Type III cyclic nucleotide phosphodiesterases and **insulin** action.
Manganiello V C; Degerman E; Taira M; Kono T; Belfrage P
Laboratory of Cellular Metabolism, NHLBI, National Institutes of Health, Bethesda, Maryland 20892, USA.
Current topics in cellular regulation (UNITED STATES) **1996**, 34 p63-100, ISSN 0070-2137 Journal Code: 2984740R
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

9/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10332179 96134479 PMID: 8527305
The effects of wortmannin, a potent **inhibitor** of phosphatidylinositol 3-**kinase**, on **insulin**-stimulated glucose transport, GLUT4 translocation, antilipolysis, and DNA synthesis.
Evans J L; Honer C M; Womelsdorf B E; Kaplan E L; Bell P A
Diabetes Department, Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, East Hanover, NJ 07936, USA.
Cellular signalling (ENGLAND) May **1995**, 7 (4) p365-76, ISSN 0898-6568 Journal Code: 8904683
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
PI 3-**kinase** , an enzyme that selectively phosphorylates the 3-position of the inositol ring, is acutely activated by **insulin** and other growth factors. The physiological significance of PI 3-**kinase** activation and, more specifically, its role in **insulin** action is an area under intense investigation. In this study, we have examined the role of PI 3-**kinase** activation in mediating selected metabolic and mitogenic effects of **insulin** employing the fungal metabolite wortmannin, a potent **inhibitor** of PI 3-**kinase** activity. In isolated rat and cultured 3T3-L1 adipocytes, wortmannin **inhibited** **insulin** -stimulated glucose transport (IC50 = 9 nM) without a significant effect on basal transport. **Insulin** -stimulated translocation of GLUT4 in isolated rat adipocytes was markedly **inhibited** by wortmannin. Wortmannin had no effect on either basal or **insulin** -stimulated glucose utilization in L6 myocytes, a skeletal muscle cell line in which GLUT1 is the predominant transporter isoform. Wortmannin also partially antagonized the antilipolytic effect of **insulin** on adenosine deaminase-stimulated **lipolysis** in isolated rat adipocytes. Furthermore, wortmannin caused a significant reduction in **insulin** -stimulated DNA synthesis in Fao rat hepatoma cells. We conclude that PI 3-**kinase** activation is necessary for maximum **insulin** -stimulated glucose transport, translocation of GLUT4, antilipolysis and DNA synthesis.

9/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08642774 95331367 PMID: 7607300
Tannic acid **inhibits** **insulin**-stimulated lipogenesis in rat adipose tissue and **insulin** receptor function in vitro.
Ong K C; Khoo H E; Das N P
Department of Biochemistry, National University of Singapore.
Experientia (SWITZERLAND) Jun 14 **1995**, 51 (6) p577-84, ISSN 0014-4754 Journal Code: 0376547
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Tannins occur naturally in relatively abundant amounts in fruits, herbal medicines and common beverages. Thus an understanding of how these polyphenols affect peptide hormone action is of importance. We report here that tannic acid (a hydrolysable tannin) **inhibits** **insulin** -stimulated lipogenesis in rat adipose tissue in vitro, with an IC50 estimated to be about 350 microM. However, its monomer, gallic acid, did not show a similar **inhibitory** effect at concentrations up to 1 mM. The **inhibition** by tannic acid was less evident with higher concentrations of bovine serum albumin in the incubation buffer. This was attributed to the formation of a tannin-protein complex between bovine serum albumin and tannic acid. In a binding assay, it was observed that the specific binding of **insulin** to its receptor was not **inhibited** by tannic acid in the concentration range 0-200 microM. However, **insulin**-stimulated autophosphorylation of the **insulin** receptor, and receptor-associated tyrosine **kinase** phosphorylation of RR-SRC peptide, were **inhibited** by tannic acid at concentrations as low as 25 microM. Our data do not support the current speculation that tannins affect the activity of peptide hormones by binding to them. Therefore, our finding opens up a new perspective in the understanding of the mode of action of tannins on such hormones.

9/3,AB/27 (Item 27 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08546448 95234747 PMID: 7718614
Evidence for the key role of the adipocyte cGMP-**inhibited** cAMP phosphodiesterase in the antilipolytic action of **insulin**.
Eriksson H; Ridderstrale M; Degerman E; Ekholm D; Smith C J; Manganiello V C; Belfrage P; Tornqvist H
Department of Medical and Physiological Chemistry, University of Lund, Sweden.
Biochimica et biophysica acta (NETHERLANDS) Apr 6 **1995**, 1266 (1) p101-7, ISSN 0006-3002 Journal Code: 0217513
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Enhancement of cAMP degradation by increased cGMP-**inhibited** cAMP phosphodiesterase (cGI-PDE) activity is thought to be an important component of the mechanism whereby **insulin** counteracts catecholamine-induced **lipolysis** in adipocytes. In this study the selective cGI-PDE **inhibitor** OPC3911 was used to evaluate this role of cGI-PDE activation in intact rat adipocytes with special reference to changes in cAMP levels measured as cAMP-dependent protein **kinase** (cAMP-PK) activity ratios. OPC3911 completely blocked (IC50 = 0.3 microM) the maximal **inhibitory** effect of **insulin** on noradrenaline-induced **lipolysis** and the net dephosphorylation of hormone-sensitive lipase and other intracellular target proteins for **insulin** action, whereas **insulin** -induced lipogenesis was not changed. The effect of OPC3911 on cAMP-PK activity ratios at different levels of **lipolysis** achieved by noradrenaline stimulation revealed that the reduction of cAMP-PK caused by 1 nM **insulin** was completely blocked by 3 microM OPC3911. The effect of OPC3911 was not due to an excessive increase in cellular cAMP resulting in 'supramaximal' **lipolysis** unresponsive to **insulin**. These data demonstrate that reduction in cAMP levels by the activation of cGI-PDE may be sufficient to account for the antilipolytic action of **insulin**.

9/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08310503 94380114 PMID: 8093111
Stimulation of glucose utilization in 3T3 adipocytes and rat diaphragm in vitro by the sulphonylureas, glimepiride and glibenclamide, is correlated with modulations of the cAMP regulatory cascade.
Muller G; Wied S; Wetekam E M; Crecelius A; Unkelbach A; Punter J
Hoechst Aktiengesellschaft Frankfurt a.M., SBU Metabolic Diseases H825, Frankfurt am Main, Germany.
Biochemical pharmacology (ENGLAND) Aug 30 **1994**, 48 (5) p985-96 , ISSN 0006-2952 Journal Code: 0101032
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The long-term hypoglycemic activity of sulphonylurea drugs has been attributed, in part at least, to the stimulation of glucose utilization in extra-pancreatic tissues. The novel sulphonylurea, glimepiride, gives rise to a longer lasting reduction in the blood sugar level in dogs and rabbits compared to glibenclamide (Geisen K, Drug Res 38: 1120-1130, 1988). This cannot be explained adequately by elevated plasma **insulin** levels. This study investigated whether this prolonged hypoglycemic phase was based on the drug's abilities to stimulate glucose utilization and affect the underlying regulatory mechanisms in **insulin**-sensitive cells in vitro.

It was found that in the absence of added **insulin**, glimepiride and glibenclamide (1-50 microM) stimulated lipogenesis (3T3 adipocytes) and glycogenesis (isolated rat diaphragm) approximately 4.5- and 2.5-fold, respectively, and reduced the isoproterenol-stimulated **lipolysis** (rat adipocytes) up to 40-60%. The increased glucose utilization was correlated with a 3-4-fold higher 2-deoxyglucose transport rate and amount of GLUT4 at the plasma membrane, as well as with increased activities of key metabolic enzymes (glycerol-3-phosphate acyltransferase, glycogen synthase) within the same concentration range. Furthermore, the low Km cAMP-specific phosphodiesterase was activated 1.8-fold, whereas the cytosolic cAMP level and protein **kinase** A activity ratios were significantly lowered after incubation of isoproterenol-stimulated rat adipocytes with the sulphonylureas. In many of the aspects studied the novel sulphonylurea, glimepride, exhibited slightly lower ED50-values than glibenclamide. This study demonstrates correlations existing between drug-induced stimulation of glucose transport/metabolism and cAMP degradation/protein **kinase** A **inhibition** as well as between the relative efficiencies of glimepiride and glibenclamide in inducing these extra-pancreatic processes. Therefore, it is suggested that the stimulation of glucose utilization by sulphonylureas is mediated by a decrease of cAMP-dependent phosphorylation of GLUT4 and glucose metabolizing enzymes. The therapeutic relevance of extra-pancreatic effects of sulphonylureas, in general, and of the differences between glimepiride and glibenclamide as observed in vitro in this work, in particular, remain to be elucidated.

9/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08288579 94354818 PMID: 8074671
PI-3-**kinase** **inhibitor** Wortmannin blocks the **insulin**-like effects of growth hormone in isolated rat adipocytes.
Ridderstrale M; Tornqvist H
Department of Paediatrics, University of Lund, Sweden.
Biochemical and biophysical research communications (UNITED STATES) Aug 30 **1994**, 203 (1) p306-10, ISSN 0006-291X Journal Code: 0372516
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effect of wortmannin, a selective phosphatidylinositol 3-**kinase** **inhibitor**, on the **insulin**-like effects of growth hormone in isolated adipocytes from rat was investigated. Wortmannin **inhibited** both the lipogenic and the antilipolytic effects (IC50 approximately 20 nM) with no effect on [125I]-growth hormone binding to the adipocytes. These data suggest that phosphatidylinositol 3-**kinase** might play an important role in the **insulin**-like actions of growth hormone.

9/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08283885 94350123 PMID: 8070584
Essential role of phosphatidylinositol 3-**kinase** in **insulin**-induced activation and phosphorylation of the cGMP-**inhibited** cAMP phosphodiesterase in rat adipocytes. Studies using the selective **inhibitor** wortmannin.
Rahn T; Ridderstrale M; Tornqvist H; Manganiello V; Fredrikson G; Belfrage P; Degerman E
Department of Medical and Physiological Chemistry, University of Lund, Sweden.
FEBS letters (NETHERLANDS) Aug 22 **1994**, 350 (2-3) p314-8,

ISSN 0014-5793 Journal Code: 0155157
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Incubation of rat adipocytes with wortmannin, a potent and selective phosphatidylinositol 3-**kinase** (PI 3-**kinase**) **inhibitor**, completely blocked the antilipolytic action of **insulin** (IC50 = 100 nM), the **insulin**-induced activation and phosphorylation of cGMP-**inhibited** cAMP phosphodiesterase (cGI-PDE) as well as the activation of the **insulin**-stimulated cGI-PDE **kinase** (IC50 = 10-30 nM). No direct effects of the **inhibitor** on the **insulin**-stimulated cGI-PDE **kinase**, the cGI-PDE and the hormone-sensitive lipase were observed. These data suggest that activation of PI 3-**kinase** upstream of the **insulin**-stimulated cGI-PDE **kinase** in the antilipolytic **insulin** signalchain has an essential role for **insulin**-induced cGI-PDE activation/phosphorylation and anti-**lipolysis**.

9/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08261624 94327646 PMID: 8051164
The phosphatidylinositol 3-**kinase** serine **kinase** phosphorylates IRS-1. Stimulation by **insulin** and **inhibition** by Wortmannin.
Lam K; Carpenter C L; Ruderman N B; Friel J C; Kelly K L
Evans Department of Medicine, Boston University Medical Center, Massachusetts 02118.
Journal of biological chemistry (UNITED STATES) Aug 12 **1994**, 269 (32) p20648-52, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: DK42621; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Phosphatidylinositol 3-**kinase** (PI 3-**kinase**) is a heterodimer composed of an 85-kDa subunit that binds tyrosyl-phosphorylated proteins via its SH2 domains and a 110-kDa catalytic subunit. Expression and mutagenesis experiments have shown that the 110-kDa subunit is a dual specificity **kinase** that possesses both lipid and serine **kinase** activities. Except for the 85- and 110-kDa subunits of PI 3-**kinase**, however, no endogenous substrates for the serine **kinase** have been identified. The results of the present study show that another target of this **kinase** is the **insulin** receptor substrate, IRS-1. Serine phosphorylation of IRS-1 as well as the 85-kDa subunit of PI 3-**kinase** was demonstrated in immunoprecipitates of PI 3-**kinase** and IRS-1 isolated from rat adipocytes incubated with **insulin**. In adipocytes incubated in the absence of **insulin**, only the serine phosphorylation of p85 was observed in immunoprecipitates of PI 3-**kinase**. Both the serine and lipid **kinase** activities of PI 3-**kinase** were abolished by the fungal metabolite Wortmannin. Wortmannin also partially **inhibited** the ability of **insulin** to stimulate glucose transport and **inhibit** **lipolysis** in fat cells. These data raise the possibility that the serine **kinase** activity of PI 3-**kinase** is involved in **insulin** signaling. They also suggest that **inhibition** of the lipid or serine **kinase** activities of PI 3-**kinase** could explain the effect of Wortmannin to diminish **insulin** action.

9/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08178927 94244848 PMID: 8187953

Growth hormone regulation of lipid metabolism in cells transfected with growth hormone receptor cDNA.

Moller C; Emtner M; Arner P; Norstedt G
Center for Biotechnology, Karolinska Institute, Huddinge, Sweden.

Molecular and cellular endocrinology (IRELAND) Feb **1994**, 99 (1) p111-7, ISSN 0303-7207 Journal Code: 7500844
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The functional properties of the growth hormone (GH) receptor was studied using cellular transfection of GH receptor cDNA. GH treatment (1.5-2 h) of Chinese hamster ovary cells, stably transfected with GH receptor cDNA (CHO4), resulted in increased cellular lipid synthesis (240% of control). This effect was blocked by staurosporine, suggesting a dependence on cellular **kinases** . However, if GH treatment of CHO4 cells was prolonged (16 h), this instead stimulated **lipolysis** (128% of control). The GH receptor in CHO4 cells was also shown to be functional in terms of ligand internalization. A GH receptor mutant, in which 183 amino acids had been deleted in the carboxyterminal of the intracellular domain was functionally active, while a receptor without its intracellular domain was shown to be inactive. In conclusion, GH receptors expressed in CHO cells are functional and GH was also shown to have both an acute **insulin**-like effect, which was **kinase** dependent, and a long-term anti-**insulin** -like effect on the lipid metabolism. This suggests that an approach using GH receptor cDNA transfected cells can be of value in understanding the mechanism of GH action.

9/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08176166 94242087 PMID: 8185665

A dynamic system for suppression and re-expression of **insulin** and pervanadate bioresponses in rat adipocytes. Treatment with okadaic acid and staurosporine.

Shisheva A; Shechter Y
Department of Hormone Research, Weizmann Institute of Science, Rehovot, Israel.

Biochemical pharmacology (ENGLAND) Apr 29 **1994**, 47 (9) p1537-44, ISSN 0006-2952 Journal Code: 0101032
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

In previous studies, we demonstrated that while okadaic acid stimulates glucose metabolism, it suppresses the bioresponses of **insulin** itself in rat adipocytes (Shisheva and Shechter, Endocrinology 129: 2279-2288, 1991). Both stimulation and suppression were attributed to okadaic acid-dependent **inhibition** of protein phosphatases 1 and 2A. We report here that exposure of adipocytes to staurosporine prior to okadaic acid restored **insulin**-stimulated actions on glucose metabolism. The effect was half-maximal at staurosporine concentrations as low as 70 nM and was fully expressed (80-87% of the control) at 400-500 nM. Similarly, the **insulin** -like effect of pervanadate, which was also suppressed by okadaic acid, was restored completely with staurosporine pretreatment. Staurosporine was less effective in restoring cell responses **inhibited** by high concentrations of okadaic acid, or when added to the cells after okadaic acid. Cell resensitization was unique to staurosporine and could not be produced by various agents that reduce

cellular protein **kinase** A- or protein **kinase** C-dependent phosphorylation, such as phenylisopropyl adenosine (PIA), K-252a and GF 109203X. Staurosporine (400 nM) partially reversed **lipolysis** induced by okadaic acid but not that induced by beta-adrenergic stimulation. PIA, which antagonized okadaic acid-induced **lipolysis** to the same extent as staurosporine, was not capable of restoring **insulin** responses. Further studies aimed at elucidating this reversing effect revealed that staurosporine did not reactivate okadaic acid-**inhibited** protein phosphatases 1 and 2A in both cellular and cell-free systems. In summary, we report here a unique dynamic system in which **insulin** and pervanadate bioeffects can be fully suppressed and again re-expressed without reactivation of protein phosphatase 1 or 2A. The precise site for both effects, although still obscure, appears to be downstream from autophosphorylated **insulin** receptor.

9/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08083107 94148860 PMID: 8106400
Essential role of phosphatidylinositol 3-**kinase** in **insulin** -induced glucose transport and antilipolysis in rat adipocytes. Studies with a selective **inhibitor** wortmannin.
Okada T; Kawano Y; Sakakibara T; Hazeki O; Ui M
Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences, University of Tokyo, Japan.
Journal of biological chemistry (UNITED STATES) Feb 4 **1994**, 269 (5) p3568-73, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Significant activity of phosphatidylinositol 3-**kinase** (PI 3-**kinase**) was detected in the membrane fractions, or in the immunoprecipitates prepared with anti-phosphotyrosine antibodies, from rat adipocytes that had been incubated with **insulin** for 20 min. The PI 3-**kinase** activity in these preparations as well as in the whole cell lysates of adipocytes not treated with **insulin** was **inhibited** by the addition of wortmannin, a fungal metabolite, to the enzyme assay mixture. The **inhibition** was dependent on the **inhibitor** concentration with IC50 being less than 10 nM and perfect **inhibition** at 100 nM. The effect of **insulin** to induce membrane PI 3-**kinase** activity was mostly abolished, but its effects to tyrosine-phosphorylate the beta-subunit of the **insulin** receptor or other cellular substrate proteins including **insulin** -receptor-substrate-1 were not at all antagonized, by wortmannin added to the cell incubation medium. **Insulin** stimulation of cellular 2-deoxyglucose uptake and **inhibition** of isoproterenol-induced **lipolysis** observable in adipocytes under the same conditions were also antagonized by wortmannin added in the same concentration range as used for the **inhibition** of **insulin**-susceptible PI 3-**kinase** . It is concluded, therefore, that activation of wortmannin-sensitive PI 3-**kinase** plays a pivotal role in the intracellular signaling pathways arising from the **insulin** receptor autophosphorylation and leading to certain metabolic responses.

9/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07943167 94008700 PMID: 8404595
Mechanism of pervanadate stimulation and potentiation of **insulin**

-activated glucose transport in rat adipocytes: dissociation from vanadate effect.
Shisheva A; Shechter Y
Department of Hormone Research, Weizmann Institute of Science, Rehovot, Israel.
Endocrinology (UNITED STATES) Oct **1993**, 133 (4) p1562-8, ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Previous studies have shown that the combination of vanadate and H2O2 generates peroxide(s) of vanadate (pervanadate) that is able to mimic **insulin** in stimulating lipogenesis or protein synthesis and **inhibiting lipolysis** in rat adipocytes. Here we report that pervanadate is a potent trigger of 3-O-methylglucose transport in rat adipocytes, with an effective concentration of 5 microM and a maximum at 20 microM. Moreover, pervanadate produced an additional activation of approximately 60% on glucose influx in cells treated with maximally activating concentrations of **insulin** . Vanadate was ineffective in potentiating **insulin** -stimulated glucose uptake. Quercetin, a bioflavonoid that **inhibits insulin** receptor tyrosine **kinase** , blunted this effect of pervanadate. Treatment of adipocytes with pervanadate **inhibited** protein phosphotyrosyl phosphatase activity of cell extracts in a dose-dependent manner, with an ID50 of 5 microM and complete **inhibition** at 80 microM. In contrast, vanadate (1-800 microM) did not appreciably **inhibit** cell phosphotyrosyl phosphatases. The **inhibitory** effect of pervanadate correlated with the increase in protein phosphotyrosine accumulation, as determined by Western blotting with antiphosphotyrosine antibodies. The most prominent phosphotyrosine-containing band detected in pervanadate-treated adipocytes was that of autophosphorylated **insulin** receptor, identified by immunoblotting or immunoprecipitation with antiinsulin receptor antibodies. The addition of **insulin** to pervanadate-treated adipocytes (20 microM) caused a further increase (approximately 70%) in receptor autophosphorylation. In a cell-free system using partially purified **insulin** receptor devoid of tyrosine phosphatase activity, pervanadate did not stimulate the receptor autophosphorylation or interfere with the stimulating effect of **insulin** . These results suggest that 1) pervanadate triggers glucose uptake by increasing autophosphorylation of **insulin** receptor, preventing its dephosphorylation; 2) under physiological conditions, cellular protein phosphotyrosyl phosphatase activity is high, thereby significantly opposing **insulin**-mediated hexose transport; and 3) pervanadate has the unique ability to markedly increase maximal cell responsiveness in stimulating glucose transport achieved at a saturating **insulin** concentration. These findings suggest a possible clinical application in the management of glucose uptake in pathological conditions of **insulin** resistance and hyperinsulinemia.

9/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07882507 93343324 PMID: 8342695
Glucagon and **insulin** regulate **lipolysis** in trout liver by altering phosphorylation of triacylglycerol lipase.
Harmon J S; Rieniets L M; Sheridan M A
Department of Zoology, North Dakota State University, Fargo 58105.
American journal of physiology (UNITED STATES) Jul **1993**, 265 (1 Pt 2) pR255-60, ISSN 0002-9513 Journal Code: 0370511
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
Rainbow trout were used to investigate the hormonal regulation by glucagon and **insulin** of hepatic triacylglycerol (TG) lipase activation. Two purified preparations of the trout hepatic TG lipase enzyme, the 110,000-g preparation and the resuspended ammonium sulfate fraction (ASF), were activated up to 58% with (in mM) 0.5 ATP, 0.01 cAMP, 5 MgCl2, and exogenous protein **kinase** over control levels. ATP or cAMP alone had no effect on activation. Activation of the trout hepatic lipase was reversible; complete inactivation of the ASF was obtained within 3 h in the presence of exogenous phosphorylase phosphatase. Adenosine 3',5'-cyclic monophosphate (cAMP)/ATP-dependent 32P-phosphorylation of trout hepatic lipase was observed within 5 min of incubation with the cAMP/ATP-Mg2+ activation system and 25 microCi [32P]ATP. Hormonal modulation of trout hepatic lipase phosphorylation was studied in isolated hepatocytes. Hepatocytes were incubated with [32P]-monopotassium phosphate for 3 h, then exposed to mammalian glucagon (GLU). Within 5 min, increased **lipolysis** was accompanied by a 95% increase in phosphorylation of the enzyme. Mammalian **insulin** (INS) depressed GLU-stimulated phosphorylation by 56% and **inhibited** GLU-stimulated **lipolysis**. These results indicate that GLU and INS modulate **lipolysis** in trout liver by altering phosphorylation of the TG lipase enzyme.

9/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07747753 93203240 PMID: 8454619
Role of cytosolic tyrosine **kinase** in mediating **insulin**-like actions of vanadate in rat adipocytes.
Shisheva A; Shechter Y
Department of Hormone Research, Weizmann Institute of Science, Rehovot, Israel.
Journal of biological chemistry (UNITED STATES) Mar 25 **1993**, 268 (9) p6463-9, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In previous studies we have identified a cytosolic protein tyrosine **kinase** (CytPTK) in rat adipocytes that is largely activated in vanadate-pretreated cells (Shisheva, A., and Shechter, Y. (1992) FEBS Lett. 300, 93-96). We report here that staurosporine and its analog K-252a are highly potent (ID50 = 3 and 100 nM, respectively) in **inhibiting** CytPTK activity of crude cell extract or partially purified enzyme preparations. Staurosporine and K-252a were less effective by more than 2 and 1 orders of magnitude, respectively, in **inhibiting insulin** receptor-catalyzed PolyGlu4Tyr phosphorylation in cell-free experiments. Preincubation of rat adipocytes with either staurosporine or K-252a selectively blocked the action of vanadate in activating glucose incorporation into lipids and its oxidation. Thus, staurosporine **inhibited** vanadate-stimulated lipogenesis and glucose oxidation (via glycolysis and the pentose phosphate pathway) in a concentration-dependent manner with ID50 of 75 and 300 nM, respectively. **Insulin**-stimulated bioeffects were not **inhibited** at this low range of staurosporine concentration. Staurosporine had no effect on vanadate-stimulated hexose uptake or on vanadate's antilipolytic action. Using staurosporine, we probed those **insulinomimetic** agents which facilitate their biological activity via the **insulin** receptor **kinase** (**insulin**, wheat germ agglutinin, concanavalin A, and pervanadate) or via CytPTK (vanadate and to a certain degree Mn2+ and Zn2+). These results suggest that (a) vanadate facilitates its **insulin**-like actions on glucose utilization via the cytosolic tyrosine **kinase** and (b) this enzyme does not

participate in vanadate effects in stimulating hexose uptake and in **inhibiting lipolysis**. These findings explain further vanadate's post-**insulin** receptor actions and raise possible application in the management of glucose metabolism in **insulin**-independent fashion in pathological conditions.

9/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07515321 92379051 PMID: 1324726
Quercetin selectively **inhibits insulin** receptor function in vitro and the bioresponses of **insulin** and **insulinomimetic** agents in rat adipocytes.
Shisheva A; Shechter Y
Department of Hormone Research, Weizmann Institute of Science, Rehovot, Israel.
Biochemistry (UNITED STATES) Sep 1 **1992**, 31 (34) p8059-63, ISSN 0006-2960 Journal Code: 0370623
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We report here that quercetin, a naturally occurring bioflavonoid, is an effective blocker of **insulin** receptor tyrosine **kinase**-catalyzed phosphorylation of exogenous substrate. The ID50 was estimated to be 2 +/- 0.2 microM in cell-free experiments, using a partially purified **insulin** receptor and a random copolymer of glutamic acid and tyrosine as a substrate. **Insulin** -stimulated autophosphorylation of the receptor itself was not blocked by quercetin (up to 500 microM). In intact rat adipocytes, quercetin **inhibited insulin**-stimulating effects on glucose transport, oxidation, and its incorporation into lipids. **Inhibition** of lipogenesis (50%) occurred at 47 +/- 4 microM, whereas full **inhibition** was evident at 110 +/- 10 microM quercetin. In contrast, the effect of **insulin** in **inhibiting lipolysis** remained unaltered in quercetin-treated adipocytes. The **inhibitor** was devoid of general adverse cell affects. Basal activities and the ability of lipolytic agents to stimulate **lipolysis** were not affected. **Inhibition** by quercetin enabled us to evaluate which **insulinomimetic** agents are dependent on tyrosine phosphorylation of endogenous substrates for stimulating glucose metabolism. Quercetin blocked lipogenesis mediated by **insulin** , wheat germ agglutinin, and concanavalin A. The lipogenic effect of Zn2+ and Mn2+ was partially blocked, whereas that of vanadate was not affected at all.(ABSTRACT TRUNCATED AT 250 WORDS)

9/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07293206 92156137 PMID: 1310987
Genistein differentially **inhibits** postreceptor effects of **insulin** in rat adipocytes without **inhibiting** the **insulin** receptor **kinase**.
Abler A; Smith J A; Randazzo P A; Rothenberg P L; Jarett L
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104.
Journal of biological chemistry (UNITED STATES) Feb 25 **1992**, 267 (6) p3946-51, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: DK 08484; DK; NIDDK; DK 28144; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
Genistein, an isoflavone putative tyrosine **kinase inhibitor**, was used to investigate the coupling of **insulin** receptor tyrosine **kinase** activation to four metabolic effects of **insulin** in the isolated rat adipocyte. Genistein **inhibited insulin**-stimulated glucose oxidation in a concentration-dependent manner with an ID50 of 25 micrograms/ml and complete **inhibition** at 100 micrograms/ml. Genistein also prevented **insulin**'s (10(-9) M) **inhibition** of isoproterenol-stimulated **lipolysis** with an ID50 of 15 micrograms/ml and a complete effect at 50 micrograms/ml. The effect of genistein (25 micrograms/ml) was not reversed by supraphysiological (10(-7) M) **insulin** levels. In contrast, genistein up to 100 micrograms/ml had no effect on **insulin** 's (10(-9) M) stimulation of either pyruvate dehydrogenase or glycogen synthase activity. We determined whether genistein influenced **insulin** receptor beta-subunit autophosphorylation or tyrosine **kinase** substrate phosphorylation either in vivo or in vitro by anti-phosphotyrosine immunoblotting. Genistein at 100 micrograms/ml did not **inhibit insulin**'s (10(-7) M) stimulation of **insulin** receptor tyrosine autophosphorylation or tyrosine phosphorylation of the cellular substrates pp185 and pp60. Also, genistein did not prevent **insulin**-stimulated autophosphorylation of partially purified human **insulin** receptors from NIH 3T3/HIR 3.5 cells or the phosphorylation of histones by the activated receptor tyrosine **kinase** . In control experiments using either NIH 3T3 fibroblasts or partially purified membranes from these cells, genistein did **inhibit** platelet-derived growth factor's stimulation of its receptor autophosphorylation. These findings indicate the following: (a) Genistein can **inhibit** certain responses to **insulin** without blocking **insulin**'s stimulation of its receptor tyrosine autophosphorylation or of the receptor **kinase** substrate tyrosine phosphorylation. (b) In adipocytes genistein must block the stimulation of glucose oxidation and the antilipolytic effects of **insulin** at site(s) downstream from the **insulin** receptor tyrosine **kinase**. (c) The **inhibitory** effects of genistein on hormonal signal transduction cannot necessarily be attributed to **inhibition** of tyrosine **kinase** activity, unless specifically demonstrated.

9/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07275391 92138108 PMID: 1778660
Effect of anatomical site on **insulin** action and **insulin** receptor phosphorylation in isolated rat adipocytes.
Santos R F; Sztalryd C; Reaven G
Department of Medicine, Stanford University School of Medicine, California.
International journal of obesity (ENGLAND) Nov **1991**, 15 (11) p755-62, ISSN 0307-0565 Journal Code: 7703240
Contract/Grant No.: HL08506; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effects of **insulin** were evaluated on adipocytes isolated from three different anatomical sites in male, Sprague-Dawley rats: epididymal (EPI), retroperitoneal (RP), and dorsal subcutaneous (SC). The results indicated that maximal **insulin** -stimulated glucose transport was significantly lower (P less than 0.001) in cells from the SC region as compared to EPI and RP cells. In addition, the ED50 value for SC cells (259 +/- 34 pmol/l) was significantly higher than for EPI (66 +/- 5 pM) or RP

adipocytes (111 +/- 32 pmol/l). **Insulin inhibition** of catecholamine-induced **lipolysis** was also significantly greater (P less than 0.001) in EPI cells as compared to RP or SC adipocytes, and that was true when expressed in absolute or relative terms. The decrease in the ability of **insulin** to either stimulate glucose transport or **inhibit** catecholamine induced **lipolysis** in SC cells was associated with a decrease in **insulin** receptor autophosphorylation and receptor tyrosine **kinase** activity. These data show that **insulin** action on isolated adipocytes varies as a function of anatomical site, and that these changes are associated with variations in **insulin** receptor autophosphorylation and **insulin** receptor tyrosine **kinase** activity.

9/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07175019 92037338 PMID: 1657568
Effect of okadaic acid in rat adipocytes: differential stimulation of glucose and lipid metabolism and induction of refractoriness to **insulin** and vanadate.
Shisheva A; Shechter Y
Department of Hormone Research, Weizmann Institute of Science, Rehovot, Israel.
Endocrinology (UNITED STATES) Nov **1991**, 129 (5) p2279-88,
ISSN 0013-7227 Journal Code: 0375040
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **insulin** -like effects of okadaic acid (OKA) in rat adipocytes were further characterized. Okadaic acid did not alter **insulin** receptor function. This includes undisturbed **insulin** binding and receptor-mediated ligand internalization in OKA-treated cells. Also, the tyrosine **kinase** activity of the **insulin** receptor was not modified in a cell-free system. The stimulating effects of OKA were significantly increased by preincubating (40 min) the cells at 37 C. At lower temperatures (i.e. 26-30 C), OKA did not mimic **insulin**. Maximal stimulation of lipogenesis occurred at 0.5 microM and then declined at higher concentrations. The **insulin**-like effects of OKA on lipogenesis did not persist after removal of the agent by washing at 37 C. Okadaic acid maximally stimulated the incorporation of [1-14C]glucose into lipids and the oxidation of [6-14C]glucose into 14CO2, but unlike **insulin**, it had little if any effect of oxidizing [1-14C]glucose to 14CO2 or incorporating [6-14C]glucose into lipids. Okadaic acid was equivalent to **insulin** in stimulating 3-O-methyl-glucose uptake. Since the **insulin** -like effects of OKA did not persist after preincubation and washing, the effects of **insulin** in OKA-treated cells could be evaluated. The adipocytes were found to be fully refractory to the modulating actions of **insulin**. Thus, **insulin** did not stimulate glucose transport, its oxidation, or its incorporation into lipids, and failed to reverse **lipolysis** . Unresponsiveness was fully developed after 40-min preincubation at 37 C with 3 microM OKA and was half-maximal at 0.13 microM OKA. It persisted at least over a period of 150 min. The effect of OKA was restricted to the stimulating actions of **insulin** and vanadate. Basal activities were not altered, nor was the ability of the desensitized cells to respond to isoproterenol. The lack of an **insulin** -like effect of OKA on some metabolic pathways enabled us to demonstrate that OKA (0.25 microM) also rendered adipocytes fully unresponsive to **insulin** in the continuous presence of the agent. Western blotting of the 40,000 x g pellets with antibodies to phosphotyrosine revealed the appearance of a protein with an apparent mol wt of 43,000 in OKA-desensitized cells. In summary, OKA mimics some of

insulin bioeffects, but concomitantly renders the cells tolerant to the modulating action of the hormone itself.

9/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07149322 92011518 PMID: 1655732
Effects of okadaic acid on **insulin**-sensitive cAMP phosphodiesterase in rat adipocytes. Evidence that **insulin** may stimulate the enzyme by phosphorylation.
Shibata H; Robinson F W; Soderling T R; Kono T
Department of Molecular Physiology and Biophysics, School of Medicine, Vanderbilt University, Nashville, Tennessee 37232-0615.
Journal of biological chemistry (UNITED STATES) Sep 25 **1991**, 266 (27) p17948-53, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: DK 06725; DK; NIDDK; DK 19925; DK; NIDDK; DK17808; DK ; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Okadaic acid, a potent **inhibitor** of Type 1 and Type 2A protein phosphatases, was used to investigate the mechanism of **insulin** action on membrane-bound low Km cAMP phosphodiesterase in rat adipocytes. Upon incubation of cells with 1 microM okadaic acid for 20 min, phosphodiesterase was stimulated 3.7- to 3.9-fold. This stimulation was larger than that elicited by **insulin** (2.5- to 3.0-fold). Although okadaic acid enhanced the effect of **insulin**, the maximum effects of the two agents were not additive. When cells were pretreated with 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine (H-7), the level of phosphodiesterase stimulation by okadaic acid was rendered smaller, similar to that attained by **insulin**. In cells that had been treated with 2 mM KCN, okadaic acid (like **insulin**) failed to stimulate phosphodiesterase, suggesting that ATP was essential. Also, as reported previously, the effect of **insulin** on phosphodiesterase was reversed upon exposure of hormone-treated cells to KCN. This deactivation of previously-stimulated phosphodiesterase was blocked by okadaic acid, but not by **insulin**. The above KCN experiments were carried out with cells in which A-**kinase** activity was minimized by pretreatment with H-7. Okadaic acid mildly stimulated basal glucose transport and, at the same time, strongly **inhibited** the action of **insulin** thereon. It is suggested that **insulin** may stimulate phosphodiesterase by promoting its phosphorylation and that the hormonal effect may be reversed by a protein phosphatase which is sensitive to okadaic acid. The hypothetical protein **kinase** thought to be involved in the **insulin**-dependent stimulation of phosphodiesterase appears to be more H-7-resistant than A-**kinase**.

9/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07098470 91339513 PMID: 1874033
Cellular effects of growth hormone on adipocytes.
Goodman H M; Gorin E; Schwartz Y; Tai L R; Chipkin S R; Honeyman T W; Frick G P; Yamaguchi H
Department of Physiology, University of Massachusetts Medical School, Worcester 01655.
Chinese journal of physiology (TAIWAN) **1991**, 34 (1) p27-44, ISSN 0304-4920 Journal Code: 7804502
Contract/Grant No.: KD 19392; PHS

Erratum in Chin J Physiol 1991;34(2) 241
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Adipocytes are physiological targets for GH in both growing and nongrowing individuals. In adipocytes that have been deprived of GH for at least 3 h, GH initially produces a response that is characterized by increased metabolism of glucose and **inhibition** of the lipolytic effects of catecholamines. This **insulin**-like effect disappears within 2-3 h despite continued stimulation and cannot be elicited again unless cells are deprived of GH for at least 3 h. Despite refractoriness to the **insulin** -like action of GH, the lipolytic effect of GH is evident at this time. Although termination of the **insulin**-like response and induction of both refractoriness and **lipolysis** all depend upon synthesis of RNA and proteins, these 3 effects of GH appear to be neither temporally nor causally related. Scatchard analysis of ligand binding data suggests that these various effects are produced by interaction of GH with a single class of receptors. However, since modification of either the hormone or the carbohydrate moiety of the receptor can selectively attenuate either the **insulin** -like or the lipolytic response, more than one hormone receptor interaction is likely. Northern analysis indicates the presence of at least 2 alternately spliced mRNA transcripts for the GH receptor, and at least 3 different complexes are seen after GH is covalently crosslinked to intact adipocytes. Refractoriness does not result from changes in either the number or affinity of GH receptors, but may result from increased cytosolic calcium. Although the protein **kinase** C activator phorbol myristate acetate mimics both the **insulin** -like and lipolytic actions of GH, increased activity of protein **kinase** C probably does not mediate either action of GH. The intracellular mediators of the diverse actions of GH are unknown at this time.

9/3,AB/44 (Item 44 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07061472 91302374 PMID: 1649189
Hormone-sensitive cyclic GMP-**inhibited** cyclic AMP phosphodiesterase in rat adipocytes. Regulation of **insulin** - and cAMP-dependent activation by phosphorylation.
Smith C J; Vasta V; Degerman E; Belfrage P; Manganiello V C
Department of Biochemistry, University of Florence, Italy.
Journal of biological chemistry (UNITED STATES) Jul 15 **1991**, 266 (20) p13385-90, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

In 32PO4-labeled adipocytes, isoproterenol (ISO) or physiologically relevant concentrations of **insulin** rapidly increased phosphorylation of a particulate 135-kDa protein which has been identified as a cGMP-**inhibited** "low Km" cAMP phosphodiesterase (CGI-PDE) by several criteria, including selective immunoprecipitation with anti-CGI-PDE IgG (Degerman, E., Smith, C.J., Tornqvist, H., Vasta, V., Belfrage, P., and Manganiello, V.C. (1990) Proc. Natl. Acad. Sci. U.S.A. 87, 533-537). The time courses and concentration dependences for phosphorylation of CGI-PDE by ISO and **insulin** correlated with CGI-PDE activation in the presence of these agents; effects of ISO were somewhat more rapid than those of **insulin**. Adenosine deaminase, which metabolizes the adenylate cyclase **inhibitor** adenosine, also rapidly induced phosphorylation and activation of CGI-PDE. Phenylisopropyladenosine (an adenosine deaminase-resistant adenosine analog) prevented or reversed both adenosine

deaminase-stimulated phosphorylation and activation of CGI-PDE (IC50 approximately 0.2 nM). Incubation of adipocytes with 0.1 nM **insulin** in the presence of ISO rapidly produced 30-200% greater activation and phosphorylation of CGI-PDE than the expected added effects of **insulin** and ISO individually; both effects preceded the **insulin**-induced decreases in protein **kinase** A activity and **inhibition** of **lipolysis**. These and other results indicate that CGI-PDE can be phosphorylated at distinct sites and activated by cAMP-dependent and **insulin**-dependent serine **kinase**(s), that the activation state of CGI-PDE reflects its relative phosphorylation state, and that synergistic phosphorylation/activation of CGI-PDE may be important in the antilipolytic action of **insulin**.

9/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07000598 91241274 PMID: 1903598
Effects of growth hormone on fuel utilization and muscle glycogen synthase activity in normal humans.
Bak J F; Moller N; Schmitz O
Medical Endocrinological Department III, University Clinic of Internal Medicine, Aarhus, Denmark.
American journal of physiology (UNITED STATES) May **1991**, 260 (5 Pt 1) pE736-42, ISSN 0002-9513 Journal Code: 0370511
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
To examine the **insulin** antagonistic effects of growth hormone (GH), seven healthy subjects underwent, in random order, two 5-h euglycemic clamp studies with moderate hyperinsulinemia. A GH infusion (45 ng.kg-1.min-1) was given throughout one of the studies. GH **inhibited** the **insulin** -stimulated glucose disposal by 27% from 4.4 +/- 0.7 to 3.3 +/- 0.4 mg.kg-1.min-1 (P less than 0.02) and raised the nonprotein energy expenditures (NPEE) from 18.7 +/- 0.5 to 20.5 +/- 0.3 kcal.kg-1.24 h-1 (P less than 0.03). Lipid oxidation contributed 71.7 +/- 5.6% of NPEE during the GH infusion as compared with 48.7 +/- 5.2% during the control clamp (P less than 0.02). In skeletal muscle biopsies, **insulin** binding to wheat germ agglutinin-purified **insulin** receptors and **insulin** receptor **kinase** activity were unaffected by GH infusion. Glycogen synthase activation by **insulin** was **inhibited** by 41% during the GH clamp (fractional velocity 14.1 +/- 2.5 vs. 8.3 +/- 1.4%, P less than 0.03). In conclusion, GH 1) increases energy expenditures and **inhibits** glucose oxidation in favor of an increased lipid oxidation, and 2) **inhibits** **insulin** -mediated activation of the glycogen synthase in skeletal muscle biopsies by a mechanism distal to **insulin** receptor binding and **kinase** activity.

9/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06879322 91119431 PMID: 1846737
Evidence that protein **kinase** C may not be involved in the **insulin** action on cAMP phosphodiesterase: studies with electroporated rat adipocytes that were highly responsive to **insulin**.
Shibata H; Robinson F W; Benzing C F; Kono T
Department of Molecular Physiology and Biophysics, School of Medicine, Vanderbilt University, Nashville, Tennessee 37232-0615.
Archives of biochemistry and biophysics (UNITED STATES) Feb 15

1991, 285 (1) p97-104, ISSN 0003-9861 Journal Code: 0372430
Contract/Grant No.: DK 06725; DK; NIDDK; DK 19925; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Partially permeabilized rat adipocytes with a high responsiveness to **insulin** were prepared by electroporation and used to study the effect of 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine (H-7) on **insulin** actions in adipocytes. H-7 is a well-documented **inhibitor** of several protein **kinases**, including protein **kinase** C; however, it does not rapidly enter adipocytes protected with the intact plasma membrane. The cells were suspended in Buffer X [4.74 mM NaCl, 118.0 mM KCl, 0.38 mM CaCl2, 1.00 mM EGTA, 1.19 mM Mg2SO4, 1.19 mM KH2PO4, 25.0 mM Hepes/K, 20 mg/ml bovine serum albumin, and 3 mM pyruvate/Na, pH 7.4] and electroporated six times with a Gene-Pulser (from Bio-Rad) set at 25 microF and 2 kV/cm. In cells electroporated as above, **insulin** stimulated (a) membrane-bound, cAMP phosphodiesterase approximately 2.6-fold when the hormone concentration was 10 nM and (b) glucose transport activity approximately 4.5-fold when the hormone concentration was raised to 100 nM. H-7 strongly **inhibited** the actions of **insulin** on both glucose transport (apparent Ki = 0.3 mM) and cAMP phosphodiesterase (apparent Ki = 1.2 mM) in electroporated adipocytes. H-7 also **inhibited** **lipolysis** in adipocytes; the apparent Ki value for the reaction in intact cells was 0.45 mM, and that in electroporated cells was 0.075 mM. It is suggested that a certain protein **kinase** or **kinases** that are significantly sensitive to H-7 may be involved in the **insulin** -dependent stimulation of glucose transport and that of phosphodiesterase. However, protein **kinase** C (or Ca2+/phospholipid-dependent protein **kinase**) may not be involved, at least, in the hormonal action on phosphodiesterase since the apparent Ki value of H-7 for the reaction is too high.

9/3,AB/47 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11716088 BIOSIS NO.: 199800497819
Neuro-humoral regulation of **lipolysis**: Physiological and pathological aspects.
AUTHOR: Lafontan Max(a); Langin Dominique
AUTHOR ADDRESS: (a)Inserm U. 317, Inst. Louis-Bugnard, Univ. Paul-Sabatier, CHU Rangueil, Batiment L3, 31403 Toulou**France
JOURNAL: M-S (Medecine Sciences) 14 (8-9):p865-876 Aug.-Sept., **1998**
ISSN: 0767-0974
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: French; Non-English
SUMMARY LANGUAGE: French; English

ABSTRACT: **Lipolysis** in white fat cells plays a central role in the regulation of energy balance. Triacylglycerols (TAG) stored in the adipocytes are hydrolysed consecutively to hormone sensitive lipase (HSL) activation during the stimulation of **lipolysis**. HSL catalyses the hydrolysis of TAG to diacylglycerol and then to monoacylglycerol. The hydrolysis of the monoacylglycerol-fatty acid bond is assured by a monoacylglycerol lipase. HSL is phosphorylated by the cAMP-dependent protein **kinase**. Genomic organization and functional domains of rodent and human hormone-sensitive lipase have recently been studied. Acute regulation of HSL by catecholamines and **insulin** is well documented. Non-esterified fatty acids and glycerol released by adipose tissue are taken up by other tissues where they are metabolized. The local blood flow in adipose tissue modulates the mobilization and the

re-utilization of fatty acids. Local blood flow and **lipolysis** are regulated by hormonal factors and influenced by a number of physiological factors such as diets, exercise, aging and sex. **Insulin** and catecholamines are the major hormonal regulators of **lipolysis**. Their control of **lipolysis** is subjected to variations according to the anatomical localization of adipose tissue deposits. In human, **lipolysis** differs in visceral and subcutaneous deposits. **Insulin** exerts its antilipolytic action through the stimulation of adipocyte phosphodiesterase 3B. Four adrenoceptor subtypes are involved in the adrenergic regulation of white and brown fat cell **lipolysis**. The control of adenylyl cyclase activity involves stimulatory beta1-, beta2- and beta3-adrenergic receptors and **inhibitory** alpha2-adrenoceptors. Many clinical disorders are accompanied by alteration in adipocyte **lipolysis**. Alteration of hormone-sensitive lipase activity and of catecholamine-induced **lipolysis** have been reported in obesity, familial combined hyperlipidemia, **insulin** resistance syndrome and diabetes. Changes in beta- and alpha2-adrenoceptor ratios and function as well as impairment of HSL function have been proposed to explain the lipolytic disturbances.

1998

9/3,AB/48 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11130082 BIOSIS NO.: 199799751227
Multiple signaling pathways involved in the metabolic effects of **insulin**.
AUTHOR: Moule S Kelly; Denton Richard M(a)
AUTHOR ADDRESS: (a)Dep. Biochemistry, Univ. Bristol Sch. Med. Sci., University Walk, Bristol BS8 1TD**UK
JOURNAL: American Journal of Cardiology 80 (SUPPL. 3A):p41A-49A **1997**
ISSN: 0002-9149
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The metabolic effects of **insulin** are initiated by the binding of **insulin** to the extracellular domain of the **insulin** receptor within the plasma membrane of muscle and adipose and liver cells. The subsequent activation of the intracellular tyrosine protein **kinase** activity of the receptor leads to autophosphorylation of the receptor as well as phosphorylation of a number of intracellular proteins. This gives rise to the activation of Ras and phosphatidylinositol 3-**kinase** and hence to the activation of a number of serine/threonine protein **kinases**. Many of these **kinases** appear to be arranged in cascades, including a cascade that results in the activation of mitogen-activated protein **kinase** and another that may result in the activation of protein **kinase** B, leading to the **inhibition** of glycogen synthase **kinase**-3 and the activation of the 70 kiloDalton ribosomal S6 protein **kinase** (p70 S6 **kinase**). We have explored the role of these early events in the stimulation of glycogen, fatty acid, and protein synthesis by **insulin** in rat epididymal fat cells. Comparisons have been made between the metabolic effects of **insulin** and those of epidermal growth factor, since these 2 agents have contrasting effects on p70 S6 **kinase** and mitogen-activated protein **kinase**. The effects of wortmannin (which **inhibits** phosphatidylinositol 3-**kinase**), and rapamycin (which blocks the activation of p70 S6 **kinase**) have also been studied. These and other studies indicate that the mitogen-activated protein **kinase** cascade is probably not important

in the acute metabolic effects Of **insulin**, but may have a role in the regulation of gene transcription and hence the more long-term effects of **insulin**. The short-term metabolic effects of **insulin** appear to involve at least 3 distinct signaling pathways: (1) those leading to increases in glucose transport and the activation of glycogen synthase, acetyl-CoA carboxylase, eukaryotic initiation Factor-2B, and phosphodiesterase, which may involve phosphatidylinositol 3-**kinase** and protein **kinase** B; (2) those leading to some of the effects of **insulin** on protein synthesis (formation of eukaryotic initiation factor-4F complex, S6 phosphorylation, and activation of eukaryotic elongation factor-2), which may involve phosphatidylinositol 3-**kinase** and p70 S6 **kinase**; and finally, (3) that leading to the activation of pyruvate dehydrogenase, which is unique in apparently not requiring activation of phosphatidylinositol 3-**kinase**.

1997

9/3,AB/49 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10792999 BIOSIS NO.: 199799414144
Wortmannin converts **insulin** but not oxytocin from an antilipolytic to a lipolytic agent in the presence of forskolin.
AUTHOR: Fain John N(a); Gokmen-Polar Yesim; Bahouth Suleiman W
AUTHOR ADDRESS: (a)Dep. Biochem., 858 Madison, Suite G01, Univ. Tennessee, Memphis, TN 38163**USA
JOURNAL: Metabolism Clinical and Experimental 46 (1):p62-66 **1997**
ISSN: 0026-0495
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **Insulin** is an important regulator of glucose transport and **lipolysis** in adipocytes. The present studies compared the effects of **insulin** in rat adipocytes with the effects of oxytocin and peroxovanadate, which mimic some effects of **insulin**. The antilipolytic effects of peroxovanadate and oxytocin were unaffected by 500 nmol/L wortmannin, which blocked the antilipolytic action of **insulin**. However, wortmannin, which is a relatively specific **inhibitor** of phosphatidylinositol 3-**kinase**, did block most of the stimulation of glucose metabolism by peroxovanadate while having little effect on that due to oxytocin. Under appropriate conditions, it was also possible to demonstrate a lipolytic action of **insulin**, especially with low (0.1 to 1 nmol/L) concentrations of **insulin** after exposure of adipocytes to 50 nmol/L wortmannin. The data provide additional support for the hypothesis that oxytocin and peroxovanadate affect adipose tissue metabolism by mechanisms distinctly different from those involved in **insulin** action.

1997

9/3,AB/50 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09499299 BIOSIS NO.: 199497507669
Essential role of phosphatidylinositol 3-**kinase** in **insulin** -induced activation and phosphorylation of the cGMP-**inhibited** cAMP phosphodiesterase in rat adipocytes.
AUTHOR: Rahn Tova(a); Ridderstrale Martin; Tornqvist Hans; Manganiello Vincent; Fredrikson Gudrun; Belfrage Per; Degerman Eva
AUTHOR ADDRESS: (a)Dep. Med. Physiol. Chem., Univ. Lund, PO Box 94, S-221

00 Lund**Sweden
JOURNAL: FEBS Letters 350 (2-3):p314-318 **1994**
ISSN: 0014-5793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Incubation of rat adipocytes with wortmannin, a potent and selective phosphatidylinositol 3-**kinase** (PI 3-**kinase**) **inhibitor**. completely blocked the antilipolytic action of **insulin** (IC-50 apprxeq 100 nM), the **insulin**-induced activation and phosphorylation of cGMP-**inhibited** cAMP phosphodiesterase (cGI-PDE) as well as the activation of the **insulin**-stimulated cGI-PDE **kinase** (IC-50 apprxeq 10- 30 nM). No direct effects of the **inhibitor** on the **insulinstimulated** cGI-PDE **kinase**, the cGI-PDE and the hormone-sensitive lipase were observed. These data suggest that activation of PI 3-**kinase** upstream of the **insulin**-stimulated cGI-PDE **kinase** in the antilipolytic **insulin** signal chain has in essential role for **insulin**-induced cGI-PDE activation/phosphorylation and anti-**lipolysis**.

1994

9/3,AB/51 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08792985 BIOSIS NO.: 199395082336
Histamine-induced depolarization and the cyclic AMP-protein **kinase** A system in isolated guinea pig adipocytes.
AUTHOR: Kamei Chiaki; Mukai Tomohito; Tasaka Kenji(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Fac. Pharmaceutical Sci., Okayama Univ., Okayama 700**Japan
JOURNAL: Japanese Journal of Pharmacology 60 (3):p179-186 **1992**
ISSN: 0021-5198
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The relationship between histamine (Hi)-induced depolarization and the cyclic AMP system in adipocytes was studied in guinea pigs, which seem to be more sensitive than rats to Hi. Hi caused a dose-dependent depolarization in guinea pig mesenterial and epididymal adipocytes with EC-50 values of 1.69 times 10-7 M and 1.19 times 10-7 M, respectively. Guinea pig adipocytes were 280-750 times more sensitive than rat adipocytes to Hi. Isoproterenol, forskolin and 3-isobutyl-1-methylxanthine (IBMX) also caused a depolarization, and the slopes of the concentration response lines for these drugs were almost the same as that for Hi. Furthermore, pretreatment with these drugs resulted in a potentiation of Hi-induced depolarization at lower concentrations which are not effective when each drug is used alone. In addition, Hi-induced depolarization was **inhibited** by pretreatment with prostaglandin E-1 (PGE) and **insulin** dose-dependently. The content of cyclic AMP in adipocytes was increased by Hi (10-7 M) in association with a decrease in membrane potential, KT5720, a protein **kinase** A **inhibitor**, which provides no significant effect even at a concentration of 10-6 M, showed an antagonistic effect on Hi-induced depolarization.

1992

9/3,AB/52 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07791564 BIOSIS NO.: 000092084135
HORMONE-SENSITIVE CYCLIC GMP-**INHIBITED** CYCLIC AMP PHOSPHODIESTERASE IN RAT ADIPOCYTES REGULATION OF **INSULIN**-DEPENDENT AND CYCLIC AMP-DEPENDENT ACTIVATION BY PHOSPHORYLATION
AUTHOR: SMITH C J; VASTA V; DEGERMAN E; BELFRAGE P; MANGANIELLO V C
AUTHOR ADDRESS: LAB. CELL. METABOLISM, BUILD. 10, ROOM 5N-307, NHLBI, NIH, 9000 ROCKVILLE PIKE, BETHESDA, MD. 20892.
JOURNAL: J BIOL CHEM 266 (20). 1991. 13385-13390. **1991**
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: In 32PO4-labeled adipocytes, isoproterenol (ISO) or physiologically relevant concentrations of **insulin** rapidly increased phosphorylation of a particulate 135-kDa protein which has been identified as a cGMP-**inhibited** "low km" cAMP phosphodiesterase (CGI-PDE) by several criteria, including selective immunoprecipitation with anti-CGI-PDE IgG (Degerman, E., Smith, C.J. Tornqvist, H. Vasta, V., Belfrag, P., and Manganiello, V.C. (1990) Proc. Natl. Acad. Sci. U.S.A. 87, 533-537). The time courses and concentration dependences for phosphorylation of CGI-PDE by ISO and **insulin** correlated with CGI-PDE activation in the presence of these agents: effects of ISO were somewhat more rapid than those of **insulin**. Adenosine deaminase, which metabolizes the adenylate cyclase **inhibitor** adenosine, also rapidly induced phosphorylation and activation of CGI-PDE. Phenylisopropyladenosine (an adenosine deaminase-resistant adenosine analog) prevented or reversed both adenosine deaminase-stimulated phosphorylation and activation of CGI-PDE (IC50 .apprxeq. 0.1 nM). Incubation of adiopyctes with 0.1 nM **insulin** in the presence of ISO rapidly produced 30-200% greater activation and phosphorylation of CGI-PDE than the expected added efects of **insulin** and ISO individually; both effects preceded the **insulin**-induced decreases in protein **kinase** A activity and **inhibition** of lypolysis. These and other results indicate that CGI-PDE can be phosphorylated at distinct sites and activated by cAMP-dependent and **insulin** -dependent serine **kinase**(s), that the activation state of CGI-PDE reflects its relative phosphorylation state, and that synergistic phosphorylation/activation of CGI-PDE may be important in the antilipolytic action of **insulin**.

1991

9/3,AB/53 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07538965 BIOSIS NO.: 000040084754
MOLECULAR MECHANISMS IMPORTANT IN THE ANTILIPOLYTIC ACTION OF **INSULIN** PHOSPHORYLATION-ACTIVATION OF ADIPOCYTE PARTICULATE CYCLIC GMP-**INHIBITED** CYCLIC AMP PHOSPHODIESTERASE
AUTHOR: MANGANIELLO V C; SMITH C J; DEGERMAN E; TORNQVIST H; ERIKSSON H; BASCON A; BELFRAGE P
AUTHOR ADDRESS: NIH, BETHESDA, MD.
JOURNAL: SYMPOSIUM ON THE ADIPOSE CELL: A MODEL FOR INTEGRATION FOR HORMONE SIGNALLING IN THE REGULATION OF CELLULAR FUNCTION, PARK CITY, UTAH, USA, JANUARY 18-24, 1991 HELD AT THE 20TH ANNUAL MEETINGS OF THE KEYSTONE SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY. J CELL BIOCHEM SUPPL 0 (15 PART B). 1991. 8. **1991**

CODEN: JCBSD
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1991

9/3,AB/54 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07520624 BIOSIS NO.: 000091083753
EVIDENCE THAT PROTEIN **KINASE** C MAY NOT BE INVOLVED IN THE **INSULIN** ACTION ON CYCLIC AMP PHOSPHODIESTERASE STUDIES WITH ELECTROPORATED RAT ADIPOCYTES THAT WERE HIGHLY RESPONSIVE TO **INSULIN**
AUTHOR: SHIBATA H; ROBINSON F W; BENZING C F; KONO T
AUTHOR ADDRESS: DEP. MOLECULAR PHYSIOL. BIOPHYSICS, SCH. MED., VANDERBILT UNIV., NASHVILLE, TENN. 37232-0615.
JOURNAL: ARCH BIOCHEM BIOPHYS 285 (1). 1991. 97-104. **1991**
FULL JOURNAL NAME: Archives of Biochemistry and Biophysics
CODEN: ABBIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Partially permeabilized rat adipocytes with a high responsiveness to **insulin** were prepared by electroporation and used to study the effect of 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine (H-7) on **insulin** actions in adipocytes. H-7 is a well-documented **inhibitor** of several protein **kinases**, including protein **kinase** C; however, it does not rapidly enter adipocytes protected with the intact plasma membrane. The cells were suspended in Buffer X [4.74 nM NaCl, 118.0 mM KCl, 0.38 mM CaCl2, 1.00 mM EGTA, 1.19 mM Mg2SO4, 1.19 mM KH2PO4, 25.0 mM Hepes/K, 20 mg/ml bovine serum albumin, and 3 mM pyruvate/Na, pH 7.4] and electroporated six times with a Gene-Pulser (from Bio-Rad) set at 25 .mu.F and 2 kV/cm. In cells electroporated as above, **insulin** stimulated (a) membrane-bound, cAMP phosphodiesterase approximately 2.6-fold when the hormone concentration was 10 nM and (b) glucose transport activity approximately 4.15-fold when the hormone concentration was raised to 100 nM. H-7 strongly **inhibited** the actions of **insulin** on both glucose transport (apparent Ki = 0.3 mM) and cAMP phosphodiesterase (apparent Ki = 1.2 mM) in electroporated adipocytes. H-7 also **inhibited lipolysis** in adipocytes; the apparent Ki value for the reaction in intact cells was 0.45 mM, and that in electroporated cells was 0.075 mM. It is suggested that a certain protein **kinase** or **kinases** that are significantly sensitive to H-7 may be involved in the **insulin** -dependent stimulation of glucose transport and that of phosphodiesterase. However, protein **kinase** C (or Ca2+/phospholipid-dependent protein **kinase**) may not be involved, at least, in the hormonal action on phosphodiesterase since the apparent Ki value of H-7 for the reaction is too high.

1991

9/3,AB/55 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07473662 BIOSIS NO.: 000091058381
BIOCHEMICAL ABNORMALITIES IN THE HEART OF RATS FED A SUCROSE-RICH DIET IS THE LOW ACTIVITY OF THE PYRUVATE DEHYDROGENASE COMPLEX A RESULT OF INCREASED FATTY ACID OXIDATION

AUTHOR: CHICCO A; GUTMAN R; LOMBARDO Y B
AUTHOR ADDRESS: DEP. BIOCHEM., UNIV. LITORAL, SANTIAGO DEL ESTERO 2829, SANTA FE, ARGENTINA.
JOURNAL: METAB CLIN EXP 40 (1). 1991. 15-21. **1991**
FULL JOURNAL NAME: Metabolism Clinical and Experimental
CODEN: METAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have previously shown that normal Wistar rats fed for 3 weeks with an isocaloric sucrose-rich (63%) diet (SRD) develop high levels of plasma free fatty acids and increased triacylglycerol content in the myocardium. We are now reporting that these changes are accompanied by remarkably low levels of the active form of the pyruvate dehydrogenase complex (PDHa; mean .+-. SEM, 37.2% .+-. 3.7% of the total activity) when compared with levels found in hearts donated by control rats fed the standard chow diet (STD; 71.0% .+-. 2.8%; P < .01). Increased concentrations of both long-chain acyl-CoA (0.21 .+-. 0.03 v 0.06 .+-. 0.01 .mu.mol .cntdot. g dry weight-1 found in STD; P < .01) and acetyl-CoA (0.17 .+-. 0.05 v 0.09 .+-. 0.01 found in STD; P < .01), as well as a relative decrease in coenzyme A (CoASH) (0.21 .+-. 0.02 v 0.32 .+-. 0.05 from STD; P = NS), resulting in an increased acetyl-CoA/CoASH ratio (0.80 .+-. 0.13 v 0.29 .+-. 0.03 in STD; P < .01) may have stimulated the PDH **kinase**, leading in turn to an inactivation of the PDH complex. The above enzymatic and metabolic changes in the in situ heart of SRD-fed rats were still present after perfusing them for 35 minutes with a Krebs-Henseleit buffer containing 11 mmol/L glucose as the only exogenous substrate. Since the heart triacylglycerol content at the end of the perfusion was comparable in control and experimental animals, this would indicate that SRD hearts had, in fact, a higher rate of intracellular **lipolysis** in view that the latter presented a twofold higher triacylglycerol content before starting the perfusion, and that their glycerol output was twofold larger than the one recorded in hearts donated by STD rats. The addition of POCA II (a CPT-I **inhibitor**) to the perfusate (10 .mu.mol/L) led to a normalization of PDHa levels parallel to a decrease of the acetyl-CoA/CoASH ratio and a return of citrate concentrations to normal, strongly suggesting that an increased fatty acid oxidation underlies most if not all of the above metabolic abnormalities found in the heart of SRD-fed rats. The present findings lend further support to our former proposal, that this nutritionally induced syndrome may be an attractive experimental animal model for the study of some pathophysiological mechanisms involved in human non-**insulin**-dependent diabetes mellitus in general, and to gain insight into the metabolic abnormalities present in the diabetic heart in particular.

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SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2002/Nov W3
*File 155: For updating information please see Help News155. Alert
feature enhanced with customized scheduling. See HELP ALERT.
  File   5:Biosis Previews(R)  1969-2002/Dec W2
         (c) 2002 BIOSIS
*File   5: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.

      Set  Items  Description
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           11450  ERK
          2060404  INHIBIT?
      S1    7497  ERK AND INHIBIT?
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PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES
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Processing
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          599315  REVIEW
      S4     221  LIPOLYSIS AND REVIEW
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           13521  MAPK
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...completed examining records
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            8455  FFA
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? t s9/3,ab/all
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9/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13395541 21940472 PMID: 11943743
Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes.
Lewis Gary F; Carpentier Andre; Adeli Khosrow; Giacca Adria
Department of Medicine, Division of Endocrinology, University of Toronto, Canada M5G 2C4. gary.lewis@uhn.on.ca
Endocrine reviews (United States) Apr 2002, 23 (2) p201-29, ISSN 0163-769X Journal Code: 8006258
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The primary genetic, environmental, and metabolic factors responsible for causing insulin resistance and pancreatic beta-cell failure and the precise sequence of events leading to the development of type 2 diabetes are not yet fully understood. Abnormalities of triglyceride storage and **lipolysis** in insulin-sensitive tissues are an early manifestation of conditions characterized by insulin resistance and are detectable before the development of postprandial or fasting hyperglycemia. Increased free fatty acid (**FFA**) flux from adipose tissue to nonadipose tissue, resulting from abnormalities of fat metabolism, participates in and amplifies many of the fundamental metabolic derangements that are characteristic of the insulin resistance syndrome and type 2 diabetes. It is also likely to play an important role in the progression from normal glucose tolerance to fasting hyperglycemia and conversion to frank type 2 diabetes in insulin resistant individuals. Adverse metabolic consequences of increased **FFA** flux, to be discussed in this **review**, are extremely wide ranging and include, but are not limited to: 1) dyslipidemia and hepatic steatosis, 2) impaired glucose metabolism and insulin sensitivity in muscle and liver, 3) diminished insulin clearance, aggravating peripheral tissue hyperinsulinemia, and 4) impaired pancreatic beta-cell function. The precise biochemical mechanisms whereby fatty acids and cytosolic triglycerides exert their effects remain poorly understood. Recent studies, however, suggest that the sequence of events may be the following: in states of positive net energy balance, triglyceride accumulation in "fat-buffering" adipose tissue is limited by the development of adipose tissue insulin resistance. This results in diversion of energy substrates to nonadipose tissue, which in turn leads to a complex array of metabolic abnormalities characteristic of insulin-resistant states and type 2 diabetes. Recent evidence suggests that some of the biochemical mechanisms whereby glucose and fat exert adverse effects in insulin-sensitive and insulin-producing tissues are shared, thus implicating a diabetogenic role for energy excess as a whole. Although there is now evidence that weight loss through reduction of caloric intake and increase in physical activity can prevent the development of diabetes, it remains an open question as to whether specific modulation of fat metabolism will result in improvement in some or all of the above metabolic derangements or will prevent progression from insulin resistance syndrome to type 2 diabetes.

9/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08042799 94179631 PMID: 8132894
Dietary fat and adipose tissue metabolism in ruminants, pigs, and rodents: a **review**.
Chilliard Y
Laboratoire Sous-Nutrition des Ruminants, Institut National de la Recherche Agronomique, Saint Genes Champanelle, France.
Journal of dairy science (UNITED STATES) Dec 1993, 76 (12) p3897-931

, ISSN 0022-0302 Journal Code: 2985126R
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Effects of dietary fat on dairy cows are reviewed. Dietary fat did not affect gain in BW or body condition score after peak lactation but tended to increase BW loss during early lactation and body fat deposition in growing cattle. Dietary fat decreased de novo fatty acid synthesis in adipose tissue. Basal **FFA** release from adipose tissue in vitro and beta-adrenergic lipolytic responses were increased by protected polyunsaturated fatty acids. Dietary fat increased body fat in growing pigs and decreased BW loss in lactating sows. Dietary fat decreased de novo fatty acid synthesis and basal glycerol release in adipose tissue and tended to increase simultaneously beta-adrenergic lipolytic responses to increased membrane fluidity. Dietary fat increased body fat in rats. Polyunsaturated fatty acids were sometimes less efficient than saturated ones in increasing body fat. Lipoprotein lipase activity in adipose tissue generally decreased. Hepatic fatty acid synthesis was decreased sharply by polyunsaturated fatty acids, and adipose tissue response was less important. beta-Adrenergic-stimulated **lipolysis** decreased, and fatty acid esterification increased, particularly from saturated fatty acids. A trend toward insulin resistance, which was more marked with saturated fatty acids, occurred in adipose tissue.

9/3,AB/3 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08045132 BIOSIS NO.: 000093078480
METABOLIC IMPLICATIONS OF BODY FAT DISTRIBUTION
AUTHOR: BJORNTORP P
AUTHOR ADDRESS: DEP. MED. I, SAHLGREN'S HOSP., S-41345 GOTEBORG, SWED.
JOURNAL: DIABETES CARE 14 (12). 1991. 1132-1143. 1991
FULL JOURNAL NAME: Diabetes Care
CODEN: DICAD
DOCUMENT TYPE: Review
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Insulin resistance is the cornerstone for the development of non-insulin-dependent diabetes mellitus (NIDDM). Free fatty acids (FFAs) cause insulin resistance in muscle and liver and increase hepatic gluconeogenesis and lipoprotein production and perhaps decrease hepatic clearance of insulin. It is suggested that the depressing effect of insulin on circulating **FFA** concentration is dependent on the fraction derived from visceral adipocytes, which have a low responsiveness to the antilipolytic effect of insulin. Elevated secretion of cortisol and/or testosterone induces insulin resistance in muscle. This also seems to be the case for low testosterone concentrations in men. In addition, cortisol increases hepatic gluconeogenesis. Cortisol and testosterone have "permissive" effects on adipose **lipolysis** and therefore amplify lipolytic stimulation; **FFA**, cortisol, and testosterone thus have powerful combined effects, resulting in insulin resistance and increased hepatic gluconeogenesis. All these factors promoting insulin resistance are active in abdominal visceral obesity, which is closely associated with insulin resistance, NIDDM, and the "metabolic syndrome." In addition, the endocrine aberrations may provide a cause for visceral fat accumulation, probably due to regional differences in steroid-hormone-receptor density. In addition to the increased activity along the adrenocorticosteroid axis, there also seem to be signs of increased activity from the central sympathetic nervous system. These are the established endocrine consequences of hypothalamic

arousal in the defeat and defense reactions. There is some evidence that suggests an increased prevalence of psychosocial stress factors is associated with visceral distribution of body fat. Therefore, it is hypothesized that such factors might provide a background not only to a defense reaction and primary hypertension, suggested previously, but also to a defeat reaction, which contributes to an endocrine aberration leading to metabolic aberrations and visceral fat accumulation, which in turn leads to disease.

1991

ds

Set	Items	Description
S1	7497	ERK AND INHIBIT?
S2	1278	S1 AND PY<1999
S3	0	S2 AND LIPOLYSIS
S4	221	LIPOLYSIS AND REVIEW
S5	0	S4 AND MAPK
S6	185	RD S4 (unique items)
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S9	3	S6 AND FFA

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            7353  JNK
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     S12      13  S10 AND KINASE
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...completed examining records
     S13       8  RD (unique items)
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 13/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12950150   21821854   PMID: 11832353
  Downregulated IRS-1 and PPARgamma in obese women with gestational diabetes: relationship to FFA during pregnancy.
  Catalano Patrick M; Nizielski Steven E; Shao Jianhua; Preston Larraine; Qiao Liping; Friedman Jacob E
  Department of Reproductive Biology, Case Western Reserve University School of Medicine, and MetroHealth Medical Center, Cleveland, Ohio 44106, USA.
  American journal of physiology. Endocrinology and metabolism (United States) Mar 2002, 282 (3) pE522-33, ISSN 0193-1849
Journal Code: 100901226
  Contract/Grant No.: DK-50272; DK; NIDDK; HD-11089; HD; NICHD; M01-RR-80; RR; NCRR; R01-HD-22965; HD; NICHD
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Gestational diabetes mellitus (GDM) is associated with elevated postprandial free fatty acids (FFA) and insulin resistance; however, little is known about the cellular mechanisms underlying insulin resistance to suppress lipolysis during gestation. We evaluated the longitudinal changes in insulin suppression of FFA before pregnancy and in early (12-14 wk) and late (34-36 wk) gestation in obese subjects with normal glucose tolerance and in obese GDM subjects. Abdominal subcutaneous adipose tissue biopsies were also obtained during cesarean delivery from normal obese pregnant (Preg-Con), GDM, and nonpregnant obese control (Non-Preg-Con) subjects during gynecological surgery. GDM subjects had higher basal plasma FFA before pregnancy (P = 0.055). Insulin's ability to suppress FFA levels declined from early to late gestation
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in both GDM and Preg-Con subjects and was significantly less in GDM subjects compared with Preg-Con subjects over time (P = 0.025). Adipose tissue insulin receptor substrate (IRS)-1 protein levels were 43% lower (P = 0.02) and p85alpha subunit of phosphatidylinositol 3-**kinase** was twofold higher (P = 0.03) in GDM compared with Preg-Con subjects. The levels of peroxisome proliferator-activated receptor-gamma (PPARgamma) mRNA and protein were lower by 38% in Preg-Con (P = 0.006) and by 48% in GDM subjects (P = 0.005) compared with Non-Preg controls. Lipoprotein lipase and fatty acid-binding protein-2 mRNA levels were 73 and 52% lower in GDM compared with Preg-Con subjects (P < 0.002). Thus GDM women have decreased IRS-1, which may contribute to reduced insulin suppression of **lipolysis** with advancing gestation. Decreased PPARgamma and its target genes may be part of the molecular mechanism to accelerate fat catabolism to meet fetal nutrient demand in late gestation.

13/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11243261 21269090 PMID: 11375344

The HIV protease inhibitor nelfinavir induces insulin resistance and increases basal **lipolysis** in 3T3-L1 adipocytes.

Rudich A; Vanounou S; Riesenberg K; Porat M; Tirosh A; Harman-Boehm I; Greenberg A S; Schlaeffer F; Bashan N

S. Daniel Abraham Center for Health and Nutrition, Laboratory for Multi-Disciplinary Diabetes Research, Ben-Gurion University of the Negev, Beer-Sheva, IL-84105, Israel.

Diabetes (United States) Jun **2001**, 50 (6) p1425-31, ISSN 0012-1797 Journal Code: 0372763

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

HIV protease inhibitors (HPIs) are potent antiretroviral agents clinically used in the management of HIV infection. Recently, HPI therapy has been linked to the development of a metabolic syndrome in which adipocyte insulin resistance appears to play a major role. In this study, we assessed the effect of nelfinavir on glucose uptake and **lipolysis** in differentiated 3T3-L1 adipocytes. An 18-h exposure to nelfinavir resulted in an impaired insulin-stimulated glucose uptake and activation of basal **lipolysis** . Impaired insulin stimulation of glucose up take occurred at nelfinavir concentrations >10 micromol/l (EC(50) = 20 micromol/l) and could be attributed to impaired GLUT4 translocation. Basal glycerol and free fatty acid (**FFA**) release were significantly enhanced with as low as 5 micromol/l nelfinavir, displaying fivefold stimulation of **FFA** release at 10 micromol/l. Yet, the antilipolytic action of insulin was preserved at this concentration. Potential underlying mechanisms for these metabolic effects included both impaired insulin stimulation of protein **kinase** B Ser 473 phosphorylation with preserved insulin receptor substrate tyrosine phosphorylation and decreased expression of the **lipolysis** regulator perilipin. Troglitazone pre- and cotreatment with nelfinavir partly protected the cells from the increase in basal **lipolysis**, but it had no effect on the impairment in insulin-stimulated glucose uptake induced by this HPI. This study demonstrates that nelfinavir induces insulin resistance and activates basal **lipolysis** in differentiated 3T3-L1 adipocytes, providing potential cellular mechanisms that may contribute to altered adipocyte metabolism in treated HIV patients.

13/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11030281 21023287 PMID: 11147795

Glucagon-like peptide 1 stimulates **lipolysis** in clonal pancreatic beta-cells (HIT).

Yaney G C; Civelek V N; Richard A M; Dillon J S; Deeney J T; Hamilton J A ; Korchak H M; Tornheim K; Corkey B E; Boyd A E

Evans Department of Medicine, Boston Medical Center, Massachusetts 02118, USA.

Diabetes (United States) Jan **2001**, 50 (1) p56-62, ISSN 0012-1797 Journal Code: 0372763

Contract/Grant No.: DK35914; DK; NIDDK; DK46200; DK; NIDDK; DK50662; DK; NIDDK; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Glucagon-like peptide 1 (GLP-1) is the most potent physiological incretin for insulin secretion from the pancreatic beta-cell, but its mechanism of action has not been established. It interacts with specific cell-surface receptors, generates cAMP, and thereby activates protein **kinase** A (PKA). Many changes in pancreatic beta-cell function have been attributed to PKA activation, but the contribution of each one to the secretory response is unknown. We show here for the first time that GLP-1 rapidly released free fatty acids (FFAs) from cellular stores, thereby lowering intracellular pH (pHi) and stimulating **FFA** oxidation in clonal beta-cells (HIT). Similar changes were observed with forskolin, suggesting that stimulation of **lipolysis** was a function of PKA activation in beta-cells. Triacsin C, which inhibits the conversion of FFAs to long-chain acyl CoA (LC-CoA), enhanced basal **FFA** efflux as well as GLP-1-induced acidification and efflux of FFAs from the cell. Increasing the concentration of the lipase inhibitor orlistat progressively and largely diminished the increment in secretion caused by forskolin. However, glucose-stimulated secretion was less inhibited by orlistat and only at the highest concentration tested. Because the acute addition of FFAs also increases glucose-stimulated insulin secretion, these data suggest that the incretin function of GLP-1 may involve a major role for **lipolysis** in cAMP-mediated potentiation of secretion.

13/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10844115 20407597 PMID: 10950827

Masoprocol decreases rat lipolytic activity by decreasing the phosphorylation of HSL.

Gowri M S; Azhar R K; Kraemer F B; Reaven G M; Azhar S

Stanford University School of Medicine, CA 94305, USA.

American journal of physiology. Endocrinology and metabolism (UNITED STATES) Sep **2000**, 279 (3) pE593-600, ISSN 0193-1849 Journal Code: 100901226

Contract/Grant No.: DK-46942; DK; NIDDK; DK-49705; DK; NIDDK

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Masoprocol (nordihydroguaiaretic acid), a lipoxygenase inhibitor isolated from the creosote bush, has been shown to decrease adipose tissue lipolytic activity both in vivo and in vitro. The present study was initiated to test the hypothesis that the decrease in lipolytic activity by masoprocol resulted from modulation of adipose tissue hormone-sensitive lipase (HSL) activity. The results indicate that oral administration of masoprocol to rats with fructose-induced hypertriglyceridemia significantly decreased their serum free fatty acid (**FFA**; $P < 0.05$), triglyceride (TG; $P < 0.001$), and insulin ($P < 0.05$) concentrations. In addition, isoproterenol-induced lipolytic rate and HSL activity were significantly lower ($P < 0.001$) in adipocytes isolated from masoprocol compared with

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? s py<1999 and insulin? and mapk
Processing
        21938144  PY<1999
          402338  INSULIN?
           14667  MAPK
      S1     253  PY<1999 AND INSULIN? AND MAPK
? s s1 and lipolysis
             253  S1
           14329  LIPOLYSIS
      S2       0  S1 AND LIPOLYSIS
? s lipolysis and py<1999
           14329  LIPOLYSIS
        21938144  PY<1999
      S3   11973  LIPOLYSIS AND PY<1999
? s s3 and (erk or mapk or jnk or mek)
           11973  S3
           12442  ERK
           14667  MAPK
            7907  JNK
            6559  MEK
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? s s3 and insulin?
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          402338  INSULIN?
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? s s5 and kinase?
            3273  S5
          424562  KINASE?
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? s s6 and inhibit?
             206  S6
         2105262  INHIBIT?
      S7     141  S6 AND INHIBIT?
? rd
...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
      S8      99  RD (unique items)
? s s8 and py>1990
              99  S8
        11929892  PY>1990
      S9      55  S8 AND PY>1990
? t s9/3,ab/all

 9/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

11616627   99049689   PMID: 9833943
   Regional difference in insulin inhibition of non-esterified
fatty acid release from human adipocytes: relation to insulin
 receptor phosphorylation and intracellular signalling through the
insulin receptor substrate-1 pathway.
  Zierath J R; Livingston J N; Thorne A; Bolinder J; Reynisdottir S;
Lonnqvist F; Arner P
  Department of Clinical Physiology, Karolinska Institute at Karolinska
Hospital, Sweden.
  Diabetologia (GERMANY)  Nov  1998,  41  (11)  p1343-54,  ISSN
0012-186X  Journal Code: 0006777
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
```

Increased mobilization of non-esterified fatty acids (NEFA) from visceral as opposed to peripheral fat depots can lead to metabolic disturbances because of the direct portal link between visceral fat and the liver. Compared with peripheral fat, visceral fat shows a decreased response to **insulin** . The mechanisms behind these site variations were investigated by comparing **insulin** action on NEFA metabolism with **insulin** receptor signal transduction through the **insulin** receptor substrate-1 (IRS-1) pathway in omental (visceral) and subcutaneous human fat obtained during elective surgery. **Insulin inhibited lipolysis** and stimulated NEFA re-esterification. This was counteracted by wortmannin, an **inhibitor** of phosphaditylinositol (PI) 3-**kinase**. The effects of **insulin** on antilipolysis and NEFA re-esterification were greatly reduced in omental fat cells. **Insulin** receptor binding capacity, mRNA and protein expression did not differ between the cell types. **Insulin** was four times more effective in stimulating tyrosine phosphorylation of the **insulin** receptor in subcutaneous fat cells ($p < 0.001$). Similarly, **insulin** was two to three times more effective in stimulating tyrosine phosphorylation of IRS-1 in subcutaneous fat cells ($p < 0.01$). This finding could be explained by finding that IRS-1 protein expression was reduced by 50 +/- 8% in omental fat cells ($p < 0.01$). In omental fat cells, maximum **insulin** -stimulated association of the p85 kDa subunit of PI 3-**kinase** to phosphotyrosine proteins and phosphotyrosine associated PI 3-**kinase** activity were both reduced by 50% ($p < 0.05$ or better). Thus, the ability of **insulin** to induce antilipolysis and stimulate NEFA re-esterification is reduced in visceral adipocytes. This reduction can be explained by reduced **insulin** receptor autophosphorylation and signal transduction through an IRS-1 associated PI 3-**kinase** pathway in visceral adipocytes.

9/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11562580 98454608 PMID: 9781323
Mechanisms regulating adipocyte **lipolysis**.
Carey G B
Department of Animal and Nutritional Sciences, University of New Hampshire, Durham 03824, USA.
Advances in experimental medicine and biology (UNITED STATES) **1998**, 441 p157-70, ISSN 0065-2598 Journal Code: 0121103
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Mechanisms regulating adipocyte **lipolysis** are reviewed in three stages. The first stage examines plasma membrane hormone receptors and G-proteins. The primary regulators of adipose tissue **lipolysis**, the catecholamines, bind to the alpha 2, beta 1, beta 2, and beta 3 adrenergic receptors. The alpha 2 receptor couples with Gi-proteins to **inhibit** cyclic AMP formation and **lipolysis**, while the beta receptors couple with Gs-proteins to stimulate cyclic AMP formation and **lipolysis**. The beta 1 receptor may mediate low level catecholamine stimulation, while the beta 3 receptor, which is activated by higher levels of catecholamines, may deliver a more sustained signal. The second stage examines the regulation of cyclic AMP, the intracellular messenger that activates protein **kinase** A. Adenylyl cyclase synthesizes cyclic AMP from ATP and is regulated by the G-proteins. Phosphodiesterase 3B hydrolyzes cyclic AMP to AMP and is activated and phosphorylated by both **insulin** and the catecholamines norepinephrine and epinephrine. The third stage focuses on the rate-limiting enzyme of **lipolysis** , hormone-sensitive lipase (HSL). This 82 to 88 kDa protein is regulated by reversible phosphorylation. Protein **kinase** A activates and phosphorylates the

enzyme at 2 sites, and 3 phosphatases have been implicated in HSL dephosphorylation. The translocation of HSL from the cytosol to the lipid droplet in response to lipolytic stimulation may be facilitated by a family of lipid-associated droplets called perilipins that are heavily phosphorylated by protein **kinase** A and dephosphorylated by **insulin**. As the mechanisms regulating adipocyte **lipolysis** continue to be uncovered, we look forward to the challenges of integrating these findings with research at the in situ and in vivo levels.

9/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11461474 98344835 PMID: 9681510
Comparison of the signaling abilities of the cytoplasmic domains of the **insulin** receptor and the **insulin** receptor-related receptor in 3T3-L1 adipocytes.
Dandekar A A; Wallach B J; Barthel A; Roth R A
Department of Molecular Pharmacology, Stanford University School of Medicine, California 94305, USA.
Endocrinology (UNITED STATES) Aug **1998**, 139 (8) p3578-84,
ISSN 0013-7227 Journal Code: 0375040
Contract/Grant No.: DK-34926; DK; NIDDK; DK-41765; DK; NIDDK
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In the present work a chimeric receptor containing the intracellular domain of the **insulin** receptor-related receptor (IRR) and the extracellular domain of the colony stimulating factor-1 (CSF-1) receptor was expressed in 3T3-L1 adipocytes and compared with the parallel chimeric receptor containing the cytoplasmic domain of the **insulin** receptor (IR). Both chimeric receptors exhibited CSF-stimulated tyrosine **kinase** activity when assayed in vitro after in vivo activation comparable to that of the endogenous IR present in these cells. No cross-activation of the expressed chimeric and endogenous receptors was observed. The cytoplasmic domain of the IRR was found to 1) mediate activation of the Ser/Thr **kinase** Akt/PKB, 2) stimulate glucose uptake, 3) **inhibit** **lipolysis** , and 4) stimulate glycogen synthase, all with a potency comparable to those of the expressed CSF-1R/IR chimera and the endogenous **insulin** receptors. These results indicate that despite the extensive differences in sequence between the cytoplasmic domains of the IRR and IR, the elements required for **insulin**-specific responses have been conserved in this distinct member of the **insulin** receptor family.

9/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11434842 98317521 PMID: 9644096
Importance of TNF-alpha and leptin in obesity and **insulin** resistance: a hypothesis on the impact of physical exercise.
Halle M; Berg A; Northoff H; Keul J
Dept. of Rehabilitation, Prevention, and Sports Medicine, Freiburg University Hospital, Germany.
Exercise immunology review (UNITED STATES) **1998**, 4 p77-94,
ISSN 1077-5552 Journal Code: 9505535
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Obesity is associated with an increased incidence of **insulin** resistance, dyslipoproteinemia, and hypercoagulability. In a more recently established hypothesis of body weight control and regulation of metabolism, the adipocyte secretes leptin and locally expresses TNF-alpha, the latter being responsible for the expression of metabolic cardiovascular risk factors. TNF-a mRNA expression and TNF-alpha protein are greatly increased in adipose tissue from obese animals and humans. Elevated TNF-alpha expression induces **insulin** resistance by downregulating the tyrosine **kinase** activity of the **insulin** receptor and decreasing the expression of GLUT-4 glucose transporters. TNF-alpha also reduces lipoprotein lipase activity in white adipocytes, stimulates hepatic **lipolysis**, and increases plasminogen activator **inhibitor**-1 content in adipocytes. Moreover, adipocytes secrete leptin, a molecule with a secondary cytokine structure whose concentrations correlate with the amount of fat tissue. Increased leptin levels downregulate appetite and increase sympathetic activity and thermogenesis in the hypothalamus. Diet-induced weight loss reduces adipose TNF-alpha expression and serum leptin levels and is associated with improved **insulin** sensitivity and lipid metabolism. Although exercise has also been shown to reduce leptin levels, an influence on TNF-a expression in adipocytes or muscle cells has not yet been demonstrated.

9/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11375346 98256309 PMID: 9593725
Association of the **insulin** receptor with phospholipase C-gamma (PLCgamma) in 3T3-L1 adipocytes suggests a role for PLCgamma in metabolic signaling by **insulin**.
Kayali A G; Eichhorn J; Haruta T; Morris A J; Nelson J G; Vollenweider P; Olefsky J M; Webster N J
UCSD/Whittier Diabetes Program, University of California San Diego, La Jolla, California 92093 and the Medical Research Service, Department of Veterans Affairs, Medical Center, San Diego, California 92161, USA.
Journal of biological chemistry (UNITED STATES) May 29 **1998**, 273 (22) p13808-18, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Phospholipase C-gamma (PLCgamma) is the isozyme of PLC phosphorylated by multiple tyrosine **kinases** including epidermal growth factor, platelet-derived growth factor, nerve growth factor receptors, and nonreceptor tyrosine **kinases**. In this paper, we present evidence for the association of the **insulin** receptor (IR) with PLCgamma. Precipitation of the IR with glutathione S-transferase fusion proteins derived from PLCgamma and coimmunoprecipitation of the IR and PLCgamma were observed in 3T3-L1 adipocytes. To determine the functional significance of the interaction of PLCgamma and the IR, we used a specific **inhibitor** of PLC, U73122, or microinjection of SH2 domain glutathione S-transferase fusion proteins derived from PLCgamma to block **insulin**-stimulated GLUT4 translocation. We demonstrate **inhibition** of 2-deoxyglucose uptake in isolated primary rat adipocytes and 3T3-L1 adipocytes pretreated with U73122. Antilipolytic effect of **insulin** in 3T3-L1 adipocytes is unaffected by U73122. U73122 selectively **inhibits** mitogen-activated protein **kinase**, leaving the Akt and p70 S6 **kinase** pathways unperturbed. We conclude that PLCgamma is an active participant in metabolic and perhaps mitogenic signaling by the **insulin** receptor in 3T3-L1 adipocytes.

9/3,AB/6 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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11289045 98167957 PMID: 9500857
Phosphorylation and activation of hormone-sensitive adipocyte phosphodiesterase type 3B.
Degerman E; Landstr m T R; Wijkander J; Holst L S; Ahmad F; Belfrage P; Manganiello V
Section for Molecular Signalling, Lund University, Lund, Sweden. Eva.Degerman@medkem.lu.se
Methods (San Diego, Calif.) (UNITED STATES) Jan **1998**, 14 (1) p43-53, ISSN 1046-2023 Journal Code: 9426302
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Phosphodiesterases (PDEs) include a large group of structurally related enzymes that belong to at least seven related gene families (PDEs 1-7) that differ in their primary structure, affinity for cAMP and cGMP, response to specific effectors, sensitivity to specific **inhibitors** , and regulatory mechanism. One characteristic of PDE3s involves their phosphorylation and activation in response to **insulin** as well as to agents that increase cAMP in adipocytes, hepatocytes, and platelets and in response to **insulin**-like growth factor 1 in pancreatic beta cells. In adipocytes, activation of the membrane-associated PDE3B is the major mechanism whereby **insulin** antagonizes catecholamine-induced **lipolysis** . PDE3B activation results in increased degradation of cAMP and, thereby, a lowering of the activity of cAMP-dependent protein **kinase** (PKA). The reduced activity of PKA leads to a net dephosphorylation and decreased activity of hormone-sensitive lipase and reduced hydrolysis of triglycerides. Activation of the rat adipocyte PDE3B by **insulin** is associated with phosphorylation of serine-302. The mechanism whereby **insulin** stimulation leads to phosphorylation/activation of PDE3B is only partly understood. In rat adipocytes, lipolytic hormones and other agents that increase cAMP, including isoproterenol, also induce rapid phosphorylation, presumably catalyzed by PKA, of serine-302 of PDE3B. The phosphorylation is associated with activation of the enzyme, most likely representing "feedback" regulation of cAMP, presumably allowing close coupling of the regulation of steady-state concentrations of both cAMP and PKA and, thereby, control of **lipolysis** . In the review we describe methods and strategies used in the authors' laboratories to study phosphorylation and activation of PDE3B in adipocytes and in vitro. Copyright 1998 Academic Press.

9/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

11146098 98022035 PMID: 9379129
Selective modification of **insulin** action in adipose tissue by hyperthyroidism.
Fryer L G; Holness M J; Sugden M C
Department of Biochemistry, Basic Medical Sciences, St Bartholomew's London, UK.
Journal of endocrinology (ENGLAND) Sep **1997**, 154 (3) p513-22, ISSN 0022-0795 Journal Code: 0375363
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Adipose-tissue **lipolysis** (assessed from glycerol release) and glucose uptake were examined in parametrial and mesenteric adipocytes prepared from control or hyperthyroid rats in relation to changes in

insulin sensitivity. Basal rates of **lipolysis** did not differ significantly between adipose-tissue depots. **Lipolysis** was maximally stimulated by noradrenaline at 1 microM, half-maximal anti-lipolytic effects of **insulin** were observed at approximately 11 microU/ ml **insulin** , and half-maximal stimulation of glucose uptake was observed at approximately 16 microU/ml **insulin** in adipocytes from both depots. Wortmannin caused a dose-dependent **inhibition** of the anti-lipolytic effect of **insulin** (150 microU/ml) on noradrenaline-stimulated **lipolysis** . Half-maximal effects of wortmannin were observed at 20-40 nM. The p70S6K **inhibitor** rapamycin and the mitogen-activated protein **kinase kinase inhibitor** PD098059 had no effects on noradrenaline-stimulated **lipolysis** . Hyperthyroidism increased basal rates of **lipolysis** and the maximal response of **lipolysis** to noradrenaline stimulation (3.1-fold, $P < 0.001$ and 2.1-fold, $P < 0.05$ respectively) in parametrial adipocytes. Hyperthyroidism markedly blunted the sensitivity of noradrenaline-stimulated **lipolysis** to half-maximal suppression by. **insulin** in both parametrial and mesenteric adipocyte depots, and noradrenaline-stimulated **lipolysis** at a maximal **insulin** concentration remained significantly higher in adipocytes prepared from hyperthyroid rats compared with controls. Hyperthyroidism had no . effect on basal and little effect on **insulin**-stimulated glucose uptake. Tri-iodothyronine administered at a low dose selectively influenced the anti-lipolytic action of **insulin** in parametrial adipocytes, and led to significantly less marked elevation in plasma non-esterified fatty acid concentrations in vivo. The results demonstrate a selective effect of hyperthyroidism to impair **insulin**'s anti-lipolytic action, and are consistent with the operation of different downstream signalling mechanisms for the effects of **insulin** on adipocyte glucose transport and **lipolysis**.

9/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11140405 98016090 PMID: 9356013
Vanadate activates membranous nonreceptor protein tyrosine **kinase** in rat adipocytes.
Elberg G; He Z; Li J; Sekar N; Shechter Y
Department of Biochemistry, Weizmann Institute of Science, Rehovot, Israel.
Diabetes (UNITED STATES) Nov **1997**, 46 (11) p1684-90, ISSN 0012-1797 Journal Code: 0372763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The **insulin**-like effects of vanadate are independent of the **insulin** receptor and **insulin** receptor substrate 1 (IRS-1) phosphorylation. A cytosolic protein tyrosine **kinase** (CytPTK), sensitive to **inhibition** by nanomolar concentrations of staurosporine (concentration at which 50% **inhibition** occurs [IC50], 1-2 nmol/l), has been implicated in some (i.e., glucose oxidation, lipogenesis) but not all (i.e., hexose uptake, **inhibition** of **lipolysis**) of the **insulin** -like effects of vanadate. We report here the existence of another nonreceptor protein tyrosine **kinase** in rat adipocytes, located exclusively in the plasma membranes (MembPTK), which we suggest is associated with hexose uptake and the antilipolytic activity of vanadate. MembPTK is a nonglycoprotein with an estimated molecular weight of 55-60 kDa. In a cell-free experiment, vanadate activates MembPTK seven- to ninefold (median effective dose, 17 +/- 2 micromol/l). Vanadate-activated MembPTK is **inhibited** by staurosporine (IC50, 60 +/- 5 nmol/l). In intact adipocytes, staurosporine antagonized vanadate-induced hexose uptake (IC50, 6.0 +/- 0.3 micromol/l) and significantly reversed the antilipolytic

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           2712  PD98059
           7445  ERK
        5185700  1
           1208  ERK(W)1
           7445  ERK
        4840963  2
            719  ERK(W)2
     S3     195  PD98059 AND (ERK (W) 1 OR ERK (W) 2)
? s3 and lipolysis?

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          13379  LIPOLYSIS?
     S4    5345  3 AND LIPOLYSIS?
? s s3 and lipolysis?

            195  S3
          13379  LIPOLYSIS?
     S5       0  S3 AND LIPOLYSIS?
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...examined 50 records  (100)
...examined 50 records  (150)
...completed examining records
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       20804581  PY<1998
     S7       7  S6 AND PY<1998
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 7/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10294611   98007754   PMID: 9349598
  Involvement of phosphoinositide 3-kinase in insulin stimulation of
MAP-kinase and phosphorylation of protein kinase-B in human skeletal
muscle: implications for glucose metabolism.
  Shepherd PR; Nave BT; Rincon J; Haigh RJ; Foulstone E; Proud C; Zierath
JR; Siddle K; Wallberg-Henriksson H
  Department of Biochemistry, University College London, UK.
  Diabetologia (GERMANY)  Oct  1997,  40  (10)  p1172-7,  ISSN
0012-186X  Journal Code: E93
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
  Isolated skeletal muscle from healthy individuals was used to evaluate
the role of phosphoinositide 3-kinase (PI 3-kinase) in insulin signalling
pathways regulating mitogen activated protein kinase (MAP-kinase) and
protein kinase-B and to investigate whether MAP-kinase was involved in
signalling pathways regulating glucose metabolism. Insulin stimulated
glycogen synthase activity (approximately 1.7 fold), increased
3-o-methylglucose transport into human skeletal muscle strips
(approximately 2 fold) and stimulated phosphorylation of the p42 ERK-
2 isoform of MAP-kinase. This phosphorylation of p42 ERK2 was not
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blocked by the PI 3-kinase inhibitors LY294002 and wortmannin although it was blocked by the MAP kinase kinase (MEK) inhibitor PD98059. However, **PD98059** (up to 20 micromol/l) did not block insulin activation of glycogen synthase or stimulation of 3-o-methylglucose transport. Wortmannin and LY294002 did block insulin stimulation of protein kinase-B (PKB) phosphorylation and stimulation of 3-o-methylglucose transport was inhibited by wortmannin (IC50 approximately 100 nmol/l). These results indicate that MAP-kinase is activated by insulin in human skeletal muscle by a PI 3-kinase independent pathway. Furthermore this activation is not necessary for insulin stimulation of glucose transport or activation of glycogen synthase in this tissue.

7/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10291104 97407913 PMID: 9261137
Insulin-like growth factor-I-mediated neurite outgrowth in vitro requires mitogen-activated protein kinase activation.
Kim B; Leventhal PS; Saltiel AR; Feldman EL
Department of Neurology and the Neuroscience Program, University of Michigan, Ann Arbor, Michigan 48109, USA.
Journal of biological chemistry (UNITED STATES) Aug 22 **1997**, 272 (34) p21268-73, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: F32 NS09912, NS, NINDS; R29 NS32843, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Insulin-like growth factor-I (IGF-I) induces neuronal differentiation in vitro. In the present study, we examined the signaling pathway underlying IGF-I-mediated neurite outgrowth. In SH-SY5Y human neuroblastoma cells, treatment with IGF-I induced concentration- and time-dependent tyrosine phosphorylation of the type I IGF receptor (IGF-IR) and extracellular signal-regulated protein kinases (**ERK**) **1** and 2. These effects of IGF-I were blocked by a neutralizing antibody against IGF-IR. Whereas IGF-IR phosphorylation was observed within 1 min, maximal phosphorylation of ERKs was not reached for 30 min. Both IGF-IR and ERK phosphorylation were maintained for at least 24 h. Also, the concentration dependence of IGF-I-stimulated IGF-IR and ERK tyrosine phosphorylation paralleled that of IGF-I-mediated neurite outgrowth. We further examined the role of mitogen-activated protein kinase activation in IGF-I-stimulated neuronal differentiation using the mitogen-activated protein kinase/ERK kinase inhibitor **PD98059**. Whereas **PD98059** had no effect on IGF-IR phosphorylation, **PD98059** reduced IGF-I-mediated ERK tyrosine phosphorylation and ERK phosphorylation of the substrate Elk-1. **PD98059** also produced a parallel reduction of IGF-I-stimulated neurite outgrowth. Finally, consistent with its ability to block neuronal differentiation, **PD98059** inhibited IGF-I-dependent changes of GAP-43 and c-myc gene expression. Together these results suggest that activation of ERKs is essential for IGF-I-stimulated neuronal differentiation.

7/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09579609 97440895 PMID: 9296354
Expression of mitogen-inducible cyclooxygenase induced by lipopolysaccharide: mediation through both mitogen-activated protein kinase and NF-kappaB signaling pathways in macrophages.
Hwang D; Jang BC; Yu G; Boudreau M
Pennington Biomedical Research Center, Louisiana State University, Baton Rouge 70808, U.S.A. hwangdh@mhs.pbrc.edu
Biochemical pharmacology (ENGLAND) Jul 1 **1997**, 54 (1) p87-96, ISSN 0006-2952 Journal Code: 9Z4
Contract/Grant No.: R01 DK-41868, DK, NIDDK

Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The mitogen-inducible cyclooxygenase (COX-2) is selectively expressed in lipopolysaccharide (LPS)-stimulated macrophages. However, the signaling pathways that lead to the expression of COX-2 in LPS-stimulated macrophages are not well understood. LPS activates members of mitogen-activated protein kinases (MAPKs) and NF-kappaB transcription factor in macrophages. We have shown that protein tyrosine kinase (PTK) inhibitors suppress the LPS-induced expression of COX-2 in macrophages (Chanmugam et al., J Biol Chem 270: 5418-5426, 1995). These PTK inhibitors also inhibit LPS-induced activation of MAPKs. Thus, in the present study, we determined whether the activation of MAPKs and NF-kappaB is necessary for the signaling pathway for the LPS-induced expression of COX-2 in the murine macrophage cell line RAW 264.7. The findings demonstrated that inhibition of extracellular signal-regulated protein kinases 1 and 2 (**ERK-1** and -2) by the selective inhibitor **PD98059** or inhibition of P38 by the specific inhibitor SB203580 results in partial suppression of COX-2 expression. However, activation of MAPKs by phorbol 12-myristate 13-acetate, H2O2, sorbitol, sodium vanadate, or a combination of these agents failed to induce the expression of COX-2. Inhibitors of NF-kappaB suppressed COX-2 expression without affecting tyrosine phosphorylation of MAPKs. The PTK inhibitors that suppressed the activation of MAPKs and COX-2 expression also inhibited the degradation of IkappaB-alpha. Together, these results indicate that the activation of NF-kappaB is required to induce the expression of COX-2 in LPS-stimulated RAW 264.7 cells. Inhibition of **ERK-1** and 2 or P38 results in partial suppression of COX-2 expression. However, the activation of MAPKs alone is not sufficient to induce the expression of COX-2 in these cells.

7/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09469914 97384862 PMID: 9242373
EGF induced SOS phosphorylation in PC12 cells involves P90 RSK-2.
Douville E; Downward J
Imperial Cancer Research Fund, London, UK.
Oncogene (ENGLAND) Jul 24 **1997**, 15 (4) p373-83, ISSN 0950-9232 Journal Code: ONC
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

SOS, the guanine nucleotide exchange factor for Ras, becomes phosphorylated on serine and threonine residues following stimulation of cells with growth factors. These phosphorylations may play a role in negative feedback of Ras stimulation and have been shown to be mediated in part by the MAP kinases **Erk-1** and **Erk-2**. Here we show that in addition to MAP kinase, a major mitogen activated kinase for SOS is p90 Rsk-2, a downstream target of MAP kinase. p90 Rsk-2 phosphorylates SOS in an in gel assay and also in solution in vitro. The ability of p90 Rsk-2 to phosphorylate SOS increases greatly following EGF treatment of PC12 cells and is blocked by expression of N17 Ras or treatment with the MEK inhibitor **PD98059**. Phosphopeptide mapping revealed that the sites phosphorylated by p90 Rsk-2 in vitro were also phosphorylated in intact cells in response to EGF treatment. Several major sites of in vivo phosphorylation correlated with p90 Rsk-2 phosphorylation sites rather than MAP kinase sites. It is therefore likely that p90 Rsk-2 plays an important role in the down regulation of the Ras activation pathway through SOS.

7/3,AB/5 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11286249 BIOSIS NO.: 19[redacted]0067581
Fibrinogen-induced cell proliferation mediated by intercellular adhesion molecule-1 (ICAM-1) requires activation of tyrosine kinases and **ERK -1**.
AUTHOR: Gardiner E E; D'Souza S E
AUTHOR ADDRESS: Joseph J. Jacobs Cent. Thrombosis, Vascular Biol./FF-2, Cleveland Clinic Foundation, Cleveland, OH**USA
JOURNAL: Blood 90 (10 SUPPL. 1 PART 1):p288A Nov. 15, **1997**
CONFERENCE/MEETING: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1997

7/3,AB/6 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11164032 BIOSIS NO.: 199799785177
Signaling molecules involved in coupling growth hormone receptor to mitogen-activated protein kinase activation.
AUTHOR: Vanderkuur Joyce A; Butch Elizabeth R; Waters Steven B; Pessin Jeffrey E; Guan Kun-Liang; Carter-Su Christin(a)
AUTHOR ADDRESS: (a)Dep. Physiol., Univ. Michigan Medical Sch., Ann Arbor, MI 48109-0622**USA
JOURNAL: Endocrinology 138 (10):p4301-4307 **1997**
ISSN: 0013-7227
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have shown previously that GH stimulates the mitogen-activated protein (MAP) kinases designated ERKs (extracellular signal-regulated kinases) 1 and 2. To examine pathways coupling GH receptor (GHR) to MAP kinase activation, we have determined the effects of GH on SHC-growth factor receptor bound 2-son of Sevenless (SHC-Grb2-SOS) association and activation of Ras, Raf, and MAP-ERK kinase (MEK). GH promoted the rapid, transient association of SHC with the Grb2-SOS complex, which correlated with the time course of Ras, Raf, and MEK activation. Despite the continuous presence of GH, these activation events were transient with Ras, Raf, and MEK returning to near basal activity by 15 or 30 min. The inactivation of Ras, Raf, and MEK directly correlated with the serine/threonine phosphorylation of SOS and dissociation of SOS from Grb2 but not Grb2 from tyrosine-phosphorylated SHC. Phosphorylation was blocked by the MEK inhibitor, **PD98059**. Based upon the established functions of the MAP kinase pathway, these data indicate that GH stimulation results in the assembly of a SHC-Grb2-SOS complex that serves to activate Ras and thereby engage the Raf-MEK-ERK pathway. Activation of this pathway generates a feedback kinase cascade that phosphorylates SOS resulting in the dissociation of SHC-Grb2 complexes from SOS, thereby causing a more rapid termination of the signaling pathway than would result from SHC dephosphorylation.

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Elevated amyloid beta protein(1-40) level induces CREB phosphorylation at

PPAR gamma-ligands inhibit migration mediated by multiple chemoattractants in vascular smooth muscle cells.

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The purpose of this study was to determine the effect of the peroxisome proliferator-activated receptor gamma-(PPAR gamma) ligands troglitazone (TRO), rosiglitazone (RSG), and 15-deoxy-delta prostaglandin J2 (15d-PGJ2) on vascular smooth muscle cell (VSMC) migration directed by multiple chemoattractants. Involvement of mitogen-activated protein kinase (**MAPK**) in migration also was examined, because TRO was previously shown to inhibit nuclear events stimulated by this pathway during mitogenic signaling in VSMCs. Migration of rat aortic VSMCs was induced 5.4-fold by PDGF, 4.6-fold by thrombin, and 2.3-fold by insulin-like growth factor I (IGF-I; all values of $p < 0.05$). The PPAR gamma ligands 15d-PGJ2, RSG, or TRO all inhibited VSMC migration with the following order of potency: 15d-PGJ2 > RSG > TRO. Inhibition of **MAPK** signaling with PD98059 completely blocked PDGF-, thrombin-, and IGF-I-induced migration. All chemoattractants induced **MAPK** activation. PPAR gamma ligands did not inhibit **MAPK** activation, suggesting a nuclear effect of these ligands downstream of **MAPK** . The importance of nuclear events was confirmed because actinomycin D also blocked migration. We conclude that PPAR gamma ligands are potent inhibitors of VSMC migration pathways, dependent on **MAPK** and nuclear events. PPAR gamma ligands act downstream of the cytoplasmic activation of **MAPK** and appear to exert their effects in the nucleus. Because VSMC migration plays an important role in the formation of atherosclerotic lesions and restenosis, PPAR gamma ligands like TRO and RSG, which ameliorate insulin resistance in humans, also may protect the vasculat

serine-133 via p44/42 MAP kinase (**Erk 1**/2)-dependent pathway in rat pheochromocytoma [redacted]2 cells.

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ABSTRACT: The deposition of amyloid beta protein (A-beta) in the cerebral cortex is the pathological characteristic of Alzheimer's disease (AD), and patients with AD suffer from progressive memory loss. Transgenic experiments have revealed that long-term memory is dependent on cyclic AMP-response element binding protein, CREB. CREB phosphorylation at serine-133 is essential for its transcriptional activity. Here we demonstrated that A-beta(1-40), at a concentration more than 1 mu-M, induced CREB phosphorylation at serine-133 in rat pheochromocytoma PC12 cells. A-beta(1-40) induced phosphorylation of p44 and p42 MAP kinases (Erk1 and Erk2) at tyrosine-204, and **PD98059**, a MEK1 inhibitor, inhibited A-beta(1-40)-induced CREB phosphorylation at serine-133. We conclude that elevated A-beta(1-40) level induces CREB phosphorylation at serine-133 via p44/42 MAP kinase-dependent pathway.